

FIG. 3

Residue	Natural Diversity	Diversity<DNA codon>	% good	%covering
L1-28	SNVDGI	SNVDGI <RDT>	100%	94%
L1-29	ISVGN	ISVG <RKT>	100%	86%
L1-29		IV <RTT>	100%	56%
L1-30	SNKGRYTDA	SNKGGRTTDAE E<RVW>	92%	93%
L1-31	SNTRIDKG	SNTRDKGG AA E<RVW>	75%	95%
L1-31		SNTRRIK <ANW>	100%	94%
L1-32	YNWFSDR	YNFSD ATIV<DHT>	55%	88%
L1-32		YFS <THT>	100%	77%
L2-50	GADWKLES	GAWLS V<KBG>	83%	67%
L2-53	SNTKIR	SNT <AVC>	100%	90%
L3-91	YSRAGH	YSA D<KMT>	75%	74%
		YS <TMT>	100%	66%
L3-92	YGNSDLTHI	YNSDTIFAV <DHT>	67%	64%
		YNSDTA <DMC>	83%	62%
L3-93	SNQTHGDR	SNTGDA <RVT>	83%	80%
		SNTDYAFIV <DHT>	44%	76%
L3-94	STWYLFAPVI	STYLFAPVINDH <NHT>	75%	78%
		STYFIN <WHT>	83%	43%
L3-96	LYWFIRP	LYFPHS <YHT>	67%	52%
		LYFIHN <HWT>	67%	58%
		LFI <HTT>	100%	42%
		LLWR <YKG>	100%	47%
		YF <TWT>	100%	29%
H1-28	TS	TSN <AVT>	67%	92%
		TS <WCC>	100%	90%
		T	100%	54%
H1-30	STNRDG	STTNRDGGAAE <RVM>	73%	96%
		STN <AVT>	100%	90%
H1-31	SNGDTRA	SNGGDTTRAEE <RVM>	91%	95%
		SNGDTA <RVT>	100%	83%
		SNGD <RRT>	100%	82%
H1-32	YSNGFA	YSNT <WMY>	75%	81%
H1-33	AYWGSNTNV	AAYWGGSSDCE* <KVK>	75%	87%
		AGSDTNVI <RNT>	87%	58%
		AYSNTN <DMT>	100%	62%
		AYSD <KMT>	100%	56%
		WG <KGG>	100%	30%
H2-50	RYWVGIEASNL	YWWVGELCDF* <KDK>	67%	49%
		RWVGASLMT <DBG>	78%	59%
		RWG <DGG>	100%	35%
		YVIASNDFT <DHT>	67%	45%
H2-52	SYNKIRDT	SYNIDTAFV <DHT>	67%	79%
		SYNNTA <DMT>	83%	77%
H2-53	SDYGHNTW	SDYHNTAP <NMT>	75%	75%
		SDYNTA <DMT>	83%	66%
H2-54	GSDNKFT	SSDKTTAEY* <DMK>	60%	47%
		SDTNAY <DMT>	67%	47%
		GSDN <RRC>	100%	81%
H2-56	STNDYEGA	SSTTNDYEA *<DMK>	90%	90%
		STNDYA <DMT>	100%	86%
H2-58	YNDRSITH	YNDSTA <DMT>	83%	77%
		YND <DAC>	100%	69%

FIG. 4A Oligo

	93	94	95	96	97	98	99	100	100a	100b	100c	101	102	length Diversity		
oligo	S	R	W	G	G	D	G	F	—	Y	A	M	D	Y	11 1.90E+06	
F59	S	R	W	G	DVK	DVK	DVK	DVK	—	DVK	A	M	D	Y	11 6.00E+08	
F63	S	R	DVK	DVK	DVK	DVK	DVK	DVK	—	DVK	A	M	D	Y	11 6.00E+07	
F64	S	R	DVK	DVK	DVK	DVK	DVK	NNK	—	Y	A	M	D	Y	12 1.10E+09	
F65	S	R	DVK	DVK	DVK	DVK	DVK	DVK	NNK	Y	A	M	D	Y	12 1.10E+09	
F59	S	R	W	G	DVK	DVK	DVK	DVK	—	DVK	A	M	D	Y	11 1.90E+06	
F63	S	R	DVK	DVK	DVK	DVK	DVK	DVK	—	DVK	A	M	D	Y	11 6.00E+08	
F64	S	R	DVK	DVK	DVK	DVK	DVK	NNK	—	Y	A	M	D	Y	11 6.00E+07	
F65	S	R	DVK	DVK	DVK	DVK	DVK	DVK	NNK	Y	A	M	D	Y	12 1.10E+09	
F66	S	R	NNK	NNK	NNK	NNK	NNK	NNK	—	Y	A	M	D	Y	11 1.10E+09	
F78	S	R	DVK	DVK	DVK	DVK	DVK	—	—	—	F	D	Y	8 1.90E+06		
F165	A	R/K	DVK	DVK	DVK	DVK	DVK	NNK	—	Y	A	M	D	Y	11 1.20E+08	
F166	A	R/K	W	NVT	DVK	DVK	DVK	DVK	—	DSG	A	M	D	Y	11 7.50E+06	
F134	A	R/K/T	NVT	NVT	NVT	NVT	NVT	NVT	—	Y	A	M	D	Y	11 2.90E+06	
F136	A	R/K/T	W	NVT	NVT	NVT	NVT	NVT	NVT	Y	A	M	D	Y	12 2.90E+06	
F137	A	R/K/T	NVT	W	NVT	NVT	NVT	NVT	NVT	Y	A	M	D	Y	12 2.90E+06	
F138	A	R/K/T	NVT	NVT	NVT	NVT	NVT	NVT	NVT	Y	A	M	D	Y	12 2.90E+06	
F142	A	R/K/T	NVT	NVT	NVT	NVT	NVT	NVT	W	Y	A	M	D	Y	12 2.90E+06	
F155	A	R/K	W	NVT	NVT	NVT	NVT	NVT	GS/AW	A	M	D	Y	12 2.30E+07		
F156	A	R/K	NVT	W	NVT	NVT	NVT	NVT	GS/AW	A	M	D	Y	12 2.30E+07		
F157	A	R/K	NVT	NVT	W	NVT	NVT	NVT	GS/AW	A	M	D	Y	12 2.30E+07		
F158	A	R/K	NVT	NVT	NVT	W	NVT	NVT	GS/AW	A	M	D	Y	12 2.30E+07		
F160	A	R/K	NVT	NVT	NVT	NVT	NVT	W	GS/AW	A	M	D	Y	12 2.30E+07		
F160g	A	R/K	NVT	NVT	NVT	NVT	NVT	NVT	W	GS/AW	A	M	D	Y	12 2.30E+07	
F165	A	R/K	DVK	DVK	DVK	DVK	DVK	NNK	—	Y	A	M	D	Y	11 1.20E+08	
F166	A	R/K	W	NVT	DVK	DVK	DVK	DVK	—	DSG	A	M	D	Y	11 7.50E+06	
F163a	A	R/K	DVK	DVK	DVK	DVK	DVK	DVK	—	KSG	A	M	D	Y	11 2.70E+08	
F164a	A	R	DVK	DVK	DVK	DVK	DVK	DVK	DVK	Y	A	M	D	Y	12 6.10E+08	
F164b	A	R	DVK	DVK	DVK	DVK	DVK	DVK	DVK	DSG	A	M	D	Y	12 3.60E+09	
F165a	A	R	DVK	DVK	DVK	DVK	DVK	DVK	DVK	DVK	Y	A	M	D	Y	13 1.10E+10
F165b	A	R	DVK	DVK	DVK	DVK	DVK	DVK	DVK	DSG	A	M	D	Y	13 6.60E+10	
F155	A	R/K	W	NVT	NVT	NVT	NVT	NVT	GS/AW	A	M	D	Y	12 2.30E+07		

Case	Age	Sex	Occupation	Education	Marital Status	Religion	Health Status	Insurance	Income	Assets	Liabilities	Net Worth	Life Expectancy	Healthcare Costs	Disability	Long-term Care	Other
F156	65	F	Retired	High School	Married	Protestant	Good	Medicare	\$25,000	\$100,000	\$50,000	\$150,000	12.5	\$1,200	No	No	None
F157	68	F	Homemaker	College	Married	Catholic	Fair	Medicare	\$18,000	\$80,000	\$40,000	\$120,000	12.0	\$1,500	No	No	None
F160	70	F	Teacher	High School	Married	Buddhist	Good	Medicare	\$30,000	\$120,000	\$60,000	\$180,000	12.8	\$1,000	No	No	None
F160g	70	F	Teacher	High School	Married	Buddhist	Good	Medicare	\$30,000	\$120,000	\$60,000	\$180,000	12.8	\$1,000	No	No	None
F167	72	F	Retired	High School	Married	Protestant	Fair	Medicare	\$22,000	\$90,000	\$45,000	\$135,000	11.5	\$1,300	No	No	None
F134	63	F	Retired	College	Married	Catholic	Good	Medicare	\$28,000	\$110,000	\$55,000	\$165,000	12.2	\$1,100	No	No	None
F135	65	F	Retired	College	Married	Catholic	Good	Medicare	\$28,000	\$110,000	\$55,000	\$165,000	12.2	\$1,100	No	No	None
F103	58	S	Student	High School	Single	Protestant	Fair	None	\$15,000	\$60,000	\$30,000	\$90,000	13.0	\$1,800	No	No	None
F66a	45	A	Student	High School	Single	Protestant	Fair	None	\$15,000	\$60,000	\$30,000	\$90,000	11.0	\$1,800	No	No	None
F66b	45	A	Student	High School	Single	Protestant	Fair	None	\$15,000	\$60,000	\$30,000	\$90,000	11.0	\$1,800	No	No	None

FIG. 4C

Oligo	93	94	95	96	97	98	99	100	100a	100b	100c	101	102	length	Diversity	
F66c	S	R	W	G	G	D	G	F	-	Y	A	M	D	Y	10	1.00E+08
F66d	A	R	NNS	NNS	NNS	NNS	NNS	NNS	Y	A/GN	M	D	Y	10	4.00E+08	
F66e	A	R	NNS	NNS	NNS	NNS	NNS	NNS	KSG	A/GN	M	D	Y	10	4.00E+08	
F66f	A	R	NNS	NNS	NNS	NNS	NNS	NNS	Y	A/GN	M	D	Y	9	3.10E+06	
F66a1	A	R	NNS	NNS	NNS	NNS	NNS	NNS	KSG	A/GN	M	D	Y	9	1.20E+07	
F66b1	A	R	NNS	NNS	NNS	NNS	NNS	NNS	Y	A/GN	M	D	Y	11	3.20E+09	
F66g	A	R	NNS	NNS	NNS	NNS	NNS	NNS	KSG	A/GN	M	D	Y	11	1.28E+10	
F66h	A	R	NNS	NNS	NNS	NNS	NNS	NNS	KSG	A/GN	M	D	Y	12	1.23E+10	
F66i	A	R	NNS	NNS	NNS	NNS	NNS	NNS	Y	A/GN	M	D	Y	12	3.28E+12	
F66j	A	R	NNS	NNS	NNS	NNS	NNS	NNS	NNS	Y	A/GN	M	D	13	1.31E+13	
F171c	A	R/K	NNK	NNK	NNK	NNK	NNK	NNK	-	-	F	D	Y	13	1.26E+13	
F171d	A	R/K	NNK	NNK	NNK	NNK	NNK	NNK	-	-	F	D	Y	8	3.20E+07	
F171e	A	R/K	NNK	NNK	NNK	NNK	NNK	NNK	-	-	F	D	Y	9	1.02E+09	
F171	A	R/K	NNK	NNK	NNK	NNK	NNK	NNK	-	-	F	D	Y	10	3.28E+10	
F185	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	-	-	F	D	Y	7	1.00E+06	
F186	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	F	D/A	F	D	Y	7		
F187	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	F	D	F	D	Y	10		
F190	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	Y	A	M	11		
F190a	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	Y	A/V/G	M	D Y 14		
F190b	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	KSG	A/V/G	M	D Y 13		
F190c	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	KSG	A/V/G	M	D Y 13		
F190d	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	KSG	A/V/G	M	D Y 14		
F190e	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	Y	A/V/G	M D Y 15	15	
	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	KSG	A/V/G	M D Y 15	15	

MRT RHSN KSG WSAG
GBT AVG GNT AVGD

FIG. 5

Light Chain Designed Diversity Diversity: $\sim 2.9 \times 10^9$

CDR-L1: diversity $\sim 7 \times 10^3$

28	29	30	31	32
RDT	RTT	RVW	RVW	DHT
D	I	D	D	A
G	V	E	E	D
I		G	G	F
N		K	K	I
S		N	N	N
V		S	S	S
		T	T	T
		R	R	V
				Y

CDR-L2: diversity = 18

50	53
KBG	AVC
A	N
G	S
L	T
S	
V	
W	

CDR-L3: diversity $\sim 2.3 \times 10^4$

91	92	93	94	96
KMT	DHT	DHT	NHT	YHT
A	A	A	A	F
D	D	D	D	H
S	F	F	F	L
Y	I	I	H	P
	N	N	I	S
	S	S	L	Y
	T	T	N	
	V	V	P	
	Y	Y	S	
			T	
			V	
			Y	

FIG. 6

Light Chain Designed Diversity
Diversity: $\sim 6.1 \times 10^8$

CDR-L1: diversity $\sim 3.4 \times 10^3$

28	29	30	31	32
RDT	RTT	RVW	ANW	THT
D	I	D	I	F
G	V	E	K	S
I		G	N	Y
N		K	R	
S		N	S	
V		S	T	
		T		
		V		

CDR-L2: diversity = 18

50	53
KBG	AVC
A	N
G	S
L	T
S	
V	
W	

CDR-L3: diversity $\sim 1.0 \times 10^4$

91	92	93	94	96
KMT	DMC	RVT	NHT	YHT
A	A	A	A	F
D	D	D	D	H
S	N	G	F	L
Y	S	N	H	P
	T	S	I	S
	Y	T	L	Y
			N	
			P	
			S	
			T	
			V	
			Y	

FIG. 7

Light Chain Designed Diversity

CDR-L3: diversity $\sim 1.3 \times 10^3$

91	92	93	94	96
TMT	DMC	RVT	WHT	HTT
S	A	A	F	F
Y	D	D	I	I
	N	G	N	L
	S	N	S	
	T	S	T	
	Y	T	Y	

FIG. 8

CDR-L1

28	29	30	31	32
RDT	RTT	RVW	RVW	DHT
D	I	D	D	A
G	V	E	E	D
I		G	G	F
N		K	K	I
S		N	N	N
V		S	S	S
		T	T	T
		V	V	V
				Y

CDR-L2

50	53
DVK	AVM
A	N
G	K
L	R
S	S
V	T2
W	

CDR-L3

91	92	93	94	96
NRT	NRT	RVM	NNK	TDK
C	C	A2	A	C
D	D	D	C	F
G	G	E	D	L
H	H	G2	E	W
N	N	K	F	Y
R	R	N	G	*
S	S	R	H	
Y	Y	S	I	
		T2	L	
			M	
			N	
			P	
			Q	
			R	
			etc	
			*	

*Amber stop codon is encoded by the degenerate codon

FIG. 9

CDR-H1

28	30	31	32	33
WCC	RVM	RVM	WMY	RNT
S	A	A	N	A
T	D	D	S	D
	E	E	T	G
	G	G	Y	I
	K	K		N
	N	N		S
	R	R		T
	S	S		V
	T	T		

CDR-H2

50	52	54	55	57	59
DBG	DHT	NMY	DMT	DMT	DMT
A	A	A	A	A	A
G	D	D	D	D	D
L	F	H	N	N	N
M	I	N	S	S	S
R	N	P	T	T	T
S	S	S	Y	Y	Y
T	T	T			
V	V	Y			
W	Y				

CDR-H3

6-8 "DVK" codons encoding
11 amino acids (ACDEGKNRSYW)

FIG. 10

CDR-H1

28	30	31	32	33
WCC	RVM	RVM	WMY	DMT
S	A	A	N	A
T	D	D	S	D
	E	E	T	N
	G	G	Y	S
	K	K		T
	N	N		Y
	R	R		
	S	S		
	T	T		

CDR-H2

50	52	54	55	57	59
DBG	DMT	DMT	RRC	DMT	DMT
A	A	A	D	A	A
G	D	D	G	D	D
L	N	N	N	N	N
M	S	S	S	S	S
R	T	T		T	T
S	Y	Y		Y	Y
T					
V					
W					

CDR-H3:

6-8 "DVK" codons encoding

11 amino acids (ACDEGKNRSYW) with 18 codons

or 5-8 "NVT" coding 12 amino acids with 12 codons
(SYCPHRTNSADG)

FIG. 11

CDR - H1

28	30	31	32	33
ACC	AVT	RVT	WMY	DMT
T	N	A	N	A
	S	D	S	D
	T	G	T	N
		N	Y	S
		S		T
		T		Y

CDR - H2

50	52	54	55	57	59
DBG	DMT	DMT	RRC	DMT	DAC
A	A	A	D	A	D
G	D	D	G	D	N
L	N	N	N	N	Y
M	S	S	S	S	
R	T	T		T	
S	Y	Y		Y	
T					
V					
W					

CDR - H3

6-8 "DVK" codons encoding

11 amino acids (ACDEG KNRSYW) with 18 codons
or 5-8 "NVT" coding 12 amino acids with 12 codons
(SYCPHRTNSADG)

CDR - L3

91	92	93	94	96
TMT	DMC	RVT	WHT	HTT
S	A	A	F	F
Y	D	D	I	I
	N	G	N	L
	S	N	S	
	T	S	T	
	Y	T	Y	

FIG. 12

CDR-H1

28	30	31	32	33
ACC	AVT	RRT	WMY	DMT
T	N	D	N	A
	S	G	S	D
	T	N	T	N
		S	Y	S
				T
				Y

CDR-H2

50	52	54	55	57	59
DBG	DMT	DMT	RRC	DMT	DAC
A	A	A	D	A	D
G	D	D	G	D	N
L	N	N	N	N	Y
M	S	S	S	S	
R	T	T		T	
S	Y	Y		Y	
T					
V					
W					

CDR-H3

6-8 "NVT" coding 11 amino acids with 12 codons
(SYCPHRTNADG) ($12^6=2.9e6$ - $12^8=4.2e8$)

CDR-L3

91	92	93	94	96
TMT	DMC	RVT	NHT	HTT
S	A	A	A	F
Y	D	D	D	I
	N	G	F	L
	S	N	H	
	T	S	I	
	Y	T	L	
			N	
			P	
			S	
			T	
			V	
			Y	

FIG. 13

CDR-H1

28	30	31	32	33
ACC	AVT	RRT	WMY	KGG/KMT
T	N	D	N	W/A
	S	G	S	G/D
	T	N	T	S
		S	Y	Y

CDR-H2

50	52	54	55	57	59
DGG/DHT	DMT	DMT	RRC	DMT	DAC
R / A	A	A	D	A	D
W /D	D	D	G	D	N
G /F	N	N	N	N	Y
I	S	S	S	S	
N	T	T		T	
S	Y	Y		Y	
T					
Y					

CDR-H3

6 "NVT" coding 11 amino acids with 12 codons
(SYCPHRTNADG) with one W walking through,
or "DVK" (SSYCWTTNKSRAADEGG*), * is stop codon

CDR-L3

91	92	93	94	96
TMT	DMC	RVT	NHT	YKG/TWT
S	A	A	A	L2/F
Y	D	D	D	W/Y
	N	G	F	R/
	S	N	H	
	T	S	I	
	Y	T	L	
			N	
			P	
			S	
			T	
			V	
			Y	

FIG. 14A

1 GAATGAGCT GTTGACAATT AATCATCGGC TCGTATAATG TGTGAAATG TGAGCGGATA ACAATTAC ACAGAAACA GCCAGTCCGT TTAGGTGTTT
CTTTACTCGA CAACTGTTAA TTAGTAGCG AGCATATTAC ACACCTTAAC ACTGCGCTAT TGTAAAGTG TGTCTTTGT CGGTAGGCA AATCCACAAA
^P_{tcac} promoter

101 TCACGAGCAC TTCACCMACA AGGACCATAG ATTATGAAAA TAAACACAGG TGCACGCATC CTCGCATTAT CCGCATTAAAC GACGATGATG TTTTCGCCT
AGTGCTCGTG AAGTGTTGT TCTTGTTATC TAATACTTTT ATTTTGTCC ACGTGGCTAG GAGCGTAATA GGCCTAAATG CTGCTACTAC AAAAGGCGGA
^Start male secretion signal

201 CGGCTTATGC ATCCGATATC CAGATGACCC AGTCCCGAG CTCCCTGTCC GCCTCTGTGG GCGATAGGT CACCATCAC TGCCGTGCCA GTCAGGATGT
GCCGATACG TAGGCTATAG GTCTACTGGG TCAGGGGCTC GAGGACAGG CCGAGACACC CGTATCCCA GTGTAGTGG ACGGCACGGT CAGTCTCTACA
^light chain start ^CDR-L1

301 GAATACTGCT GTAGCCTGGT ATCAACAGAA ACCAGGAAAA GCTCCGAAGC TTCTGATTTA CTCGGCATCC TTCTCTACT CTGGAGTCCC TTCTCGCTTC
CTTATGACGA CATCGGACCA TAGTTGTCTT TGGTCTTTT CGAGGCTTCG AAGACTAAAT GAGCCGTAGG AAGGAGATGA GACCTCAGGG AAGAGCGAAG
^CDR-L2

401 TCTGTAGCC GTTCCGGGAC GGATTTCACT CTGACCATCA GCAGTCTGCA GCGGAAGAC TTCCCAACTT ATTACTGTCA GCAACATTAT ACTACTCCTC
AGACATCG CAAGGCCCTG CCTAAAGTGA GACTGGTAGT CGTCAACGT CGGCTCTCTG AAGGTTGAA TAATCACAGT CGTTGTAATA TGATGAGGAG
^CDR-L3

501 CCACGTTCCG ACAGGTACC AAGTGGAGA TCAATCGGA TATCCGATG GCTGATCCGA ACCGTTCCG CGGTAAGAAC CTGGTTTTTC ATTCTGAGAT
GGTGCAAGCC TGTCCCATGG TTCCACCTCT AGTTAGCT ATACGGCTAC CGACTAGGT TGGCAAGGC GCCATCTTG GACCAAAAAG TAAGACTCTA
^linker ^gp-tag heavy chain start^

601 CTCCGAGGTT CAGCTGGTGG AGTCTGGCG TGGCTGTGG CAGCCAGGGG GTCACCTCG TTGTCTCTGT GCAGTTCTG GCTTCAACAT TAAAGACACC
GAGGCTCAA GTCGACCAAC TCAGACCGCC ACCGACCGCC GTCGGTCCC CGAGTGAGGC AAACAGACA CGTCAAGAC CGAAGTTGTA ATTTCTGTGG
^CDR-H1

701 TATATACACT GGGTGGCTCA GGCCCGGGT AAGGCTGG AATGGTTGC AAGGATTTAT CCTACGAATG GTTATACTAG ATATGCCGAT AGGTCGAAG
ATATATGTA CCCACGAGT CCGGGGCCCA TTCCGGGACC TTACCAACG TTCTTAATA GGATGCTTAC CAATATGATC TATACGGCTA TCGCAGTTCC
^CDR-H2

801 GCCGTTTAC TATAAGGCA GACATATCCA AAACACAGC CTACCTACAA ATGAACAGT TAAGAGCTGA GGACACTGCC GTCTATTAT GTAGCCGCTG
CGGCAAGTG ATATCGGT CTGTGTAGT TTTTGTGTGG GATGATGTT TACTTGCGA ATTTCTGACT CCTGTGACG CAGATAATAA CATCGGCGAC
^CDR-H3

901 GGGAGGGAC GGCTTCTATG CTATGGACTA CTGGGTCAA GGAACACTAG TCACCGTCTC CAGCAGTGGC GTTGGCTCTG GTTCCGGTGA TTTTGATTAT
CCCTCCCTG CGAAGATAC GATACCTGAT GACCCAGTT CTTGTGATC AGTGGCAGAG GTGCTACCG CCACGAGAC CAAGGCCACT AAAACTAATA
^start p3 C-terminal domain

FIG. 14B

1001 GAAAAGATGG CAAACGCTAA TAAGGGGGCT ATGACCGAAA ATGCCGATGA AAACGGGCTA CAGTCTGACG ACTTGATTCT GTCGCTACTG
CTTTTCTACC GTTTCGGAAT ATTCCCCCGA TACTGGCTTT TACGGCTACT TTGCGGGAT GTCCAGACTGC GATTTCGGTT TGAACATAAG CAGCGATGAC
1101 ATTACGGTGC TGCTATCGAT GGTTCATTG GTGACGTTTC CGGCCTTGCT AATGTAATG GTGCTACTGG TGATTTTGCT GGCTCTAATT CCCAAATGGC
TAATGCCACG ACGATAGCTA CCAAAGTAAC CACTGCAAG GCCGGAACGA TTACCAATTAC CACGATGACC ACTAAAACGA CCGAGATTAA GGGTTTACCG
1201 TCAAGTCGGT GAGGTGATA ATTACCTTT AATGAATAAT TTCCGTCAAT ATTTACCTTC CCTCCCTCAA TCGGTTGAAT GTCGCCCTTT TGTCTTTAGC
AGTTCAGCCA CTGCCACTAT TAAGTGGAAT TTACTTATTA AAGGCAGTTA TAAATGGAAG GGAGGGAGTT AGCCAACTTA CAGCGGGAAA ACAGAAATCG
1301 GCTGTAAC CATATGAATT TTCTATTGAT TGTGACAAAA TAACTTAT CCGTGTGTC TTGCGTTTC TTTTATATGT TGCCACCTTT ATGTATGTAT
CGACCAATTG GTATACTTAA AGATAACTA ACCTGTTTT ATTTGAATTA GGCACCACAG AAACGCAAG AAATATATA CCGGTGGAAA TACATACATA
1401 TTTCTACGTT TGCTAACATA CTGCGTAATA AGGATCTTAA A
AAAGATGCAA ACGATTGTAT GACGCATTAT TCCTCAGAAAT T
^p3 end

FIG. 15A

1 GAAATGAGCT GTTGACAATT AATCATCGGC TCGTATAATG TGTGGAATTG TGAGCGGATA ACAATTTTAC ACAGGAAACA GCCAGTCGGT TTAGGTGTTT
CCTTACTCGA CAACTGTTAA TTAGTAGCCG AGCATATTAC ACACCTTAAC ACTCGCCTAT TGTAAAGTG TGTCTTTGT CGGTACGGCA AATCCACAAA
^ptac promoter

101 TCACGAGCAC TTCACCAACA AGGACCATAG ATTATGAAA TAAACACAGG TGCACGATC CTGCAATTAT CGCATTAAC GAGCATGATG TTTTCCGGCT
AGTGCTCGTG AAGTGGTTGT TCCTGGTATC TAATACTTTT ATTTTGTCC AGTGGCTAG GAGCGTAATA GCGGTAATTG CTGCTACTAC AAAAGCGGGA
^Start male secretion signal

201 CGGCTTATGC ATCCGATATC CAGATGACCC AGTCCCGGAG CTCCTGTCC GCCTCTGTGG GCGATAGGTT CACCATCACC TGCCTGTCCTA GTCAGGATGT
GCCGAATACG TAGGCTATAG GTCTACTGGG TCAGGGGCTC GAGGGACAGG CCGAGACACC CGCTATCCCA GTGGTAGTGG ACGGCACGGT CAGTCCTTACA
^light chain start ^CDR-L1

301 GAATACTGCT GTAGCCTGGT ATCAACAGRA ACCAGGAAA GCTCCGAAGC TTCTGATTTA CTCGGCATCC TTCTCTACT CTGGAGTCCC TTCTCGCTTC
CTTATGACGA CATCGGACCA TAGTTGTCTT TGGTCTTTT CGAGGCTTCG AAGACTAAAT GAGCGTAGG AAGGAGATGA GACCTCAGGG AAGAGCGAAG
^CDR-L2

401 TCTGGTAGCC GTTCCGGGAC GGATTTTCACT CTGACCATCA GCAGCTGCA GCGGAAGAC TTGCAACTT ATTACTGTCA GCAACATTAT ACTACTCCTC
AGACCATCGG CAAGGCCCTG CCTAAAGTGA GACTGAGTGT CGTCAGACGT CGGCTTCTG AAGCGTTGAA TAATGACAGT CGTTGTAATA TGATGAGGAG
^CDR-L3

501 CCAGGTTCCG ACAGGTTACC AAGTGGAGA TCAATCGGA TATGCCGATG CTGATCCGA ACCGTTTCCG CGGTAGAAC CTGGTTTTTC ATTCTGAGAT
GGTGCAAGCC TGTCCCATGG TTCCACCTCT AGTTTAGCCT ATACGGCTAC CGACTAGGCT TGGCAAGGC GCCATTCTTG GACCAAAAAG TAAGACTCTA
^linker ^gd-tag heavy chain start^

601 CTCGAGGTT CAGCTGGTGG AGTCTGGCGG TGGCCTGGTG CAGCCAGGG GCTCACTCCG TTTGTCTCTGT GCAGCTTCTG GCTTCAACAT TAAAGACACC
GAGGCTCCAA GTCGACCACC TCAGACCGCC ACCGACCAC GTCGGTCCCC CGAGTGAGGC AAACAGGACA CGTCGAAGAC CGAAGTTGTA ATTTCTGTGG
^CDR-H1

701 TATATACACT GGGTGGTCA GGGCCCGGT AAGGGCTGG AATGGTTGC AAGGATTTAT CCTACGAATG GTTATACTAG ATATGCCGAT AGGTCGAAGG
ATATATGTGA CCCACGCAGT CCGGGGCCCA TTCCCGGACC TTACCCCAACG TTCTTAAATA GGATGCTTAC CAATATGATC TATACGCTA TCGCAGTTCC
^CDR-H2

801 GCGCTTTTAC TATAAGCGCA GACACATCCA AAAACACAGC CTACCTACAA ATGAACAGCT TAAGAGCTGA GGACACTGCC GTCTATTATT GTAGCCGCTG
CGGCAAAAGTG ATATTCCGGT CTGTGTAGT TTTTGTGTG GATGGATGTT TACTTGTGGA ATTCTGACT CCTGTGACGG CAGATAATAA CATCGGGAC
^CDR-H3

901 GGGAGGGGAC GGCTTCTATG CTATGGACTA CTGGGGTCAA GGAACACTAG TCACCGTCTC CAGCACATGC CCGCGTGGC CAGCACAGA ACTGCTGGGC
CCCTCCCTG CCGAAGATAC GATACCTGAT GACCCAGTT CCTTGTGATC AGTGGCAGAG GTCTGTAGG GCGGCACGG GTCTGTGTCT TGACGACCCG
^start zipper

FIG. 15B

```
1001 GGCCGCATGA AACAGCTAGA GGACAAGGTC GAAGAGCTAC TCTCAAGAA CTACACCTA GAGAATGAAG TGGCAAGACT CAAAAAATT GTCGGGAGC
    CCGGCGTACT TTGTCGATCT CCTGTTCCAG CTTCTCGATG AGAGGTCTT GATGGTGAT CTCTTACTTC ACCGTCTGA GTTTTTTGAA CAGCCCCCTCG

1101 GCGGAAAGCT TAGTGGCGGT GGCTCTGGTT CCGTGTGATTT TGATTATGAA AAGATGGCAA ACCTAATAA TGCCTTTTAC GCGTACTTTT
    CGCCTTTCGA ATCACCAGCA CCGAGACCAA GGCCACTAAA ACTAATACTT TTCTACCGTT TGGGATTATT CCCCCGATAC TGGCTTTTAC GGTACTTTT
    ^start p3 C-terminal domain

1201 CGCGCTACAG TCTGACGCTA AAGCAAACCT TGATTCTGTC GCTACTGATT ACGGTGCTGC TATCGATGGT TTCATTGGTG ACGTTTCCGG CCTTGCTAAT
    GCGCGATGTC AGACTGGGAT TTCGTTTGA ACTAAGACAG CGATGACTAA TGCCACGACG ATAGCTACCA AAGTAACCCAC TGCAAGGCC GGAACGATTA

1301 GGTAAATGGT CTAATGGTGA TTTTGCTGGC TCTAATTTCC AAATGGCTCA AGTCGGTGAC GGTGATAATT CACCTTTAAT GAATAATTTC CGTCAATAAT
    CCATTACCAC GATGACCACT AAAACGACCG AGATTAAAGG TTACCGAGT TCAGCCACTG CCACATAATA GTGGAAATTA CTTATTAAAG GCAGTTATAA

1401 TACCTTCCCT CCTCAATCG GTTGAATGTC GCCCTTTTGT CTTAGCGCT GGTAAACCAT ATGAATTTTC TATTGATTGT GACAAATATA ACTTATTCGG
    ATGGAAGGGA GGGAGTTAGC CAACTTACAG CGGGAATAACA GAAATCGCGA CCATTGGTA TACTTAAAG ATAATAACA CTGTTTTTAT TGAATAAGGC

1501 TGGTGTCTTT GCGTTTCTTT TATATGTTGC CACCTTTATG TATGTATTTT CTACGTTTGC TAACATACTG CGTAATAAGG AGTCTTAA
    ACCACAGAAA CGCAAGAAA ATATACAACG GTGGAATATC ATACATAAAA GATGCAACG ATTGTATGAC GCAATTATTCC TCAGAATT
    ^p3 end
```

FIG. 16A

1 GAATGAGCT GTTGACAATT AATCATCGGC TCGTAAATG TGTGGAAITG TGAGGGATA ACAAITTCAC ACAGGAACA GCCAGTCCGT TTAGTGTFT
CTTTACTCGA CAACTGTAA TTAGTAGCG AGCAATATAC ACACCTTAAC ACTCGCTAT TGTAAAGTG TGTCTTTGT CGGTACAGCA AATCCACAAA
*ptac promoter

101 TCACGAGCAC TTCACCAACA AGGACCATAG ATTATGAAA TAAACAAGG TGCACGCATC CTGCAATAT CCGCAATTAAC GAGATGATG TTTCCGCCCT
AGTGCTCGTG AAGTGGTGT TCCTGGTATC TAATACTTTT ATTTTGTC ACGTGCTAG GAGCGTAATA GCGTAATTTG CTGCTACTAC AAAGGCGGA
*start male secretion signal

201 CGGCTTATGC ATCCGATATC CAGATGACCC AGTCCCGAG CTCCTGTGCC GCTCTGTGG GCGATAGGGT CACCATCACC TCGGTGCGCA GTCAGGATGT
GCCGATACG TAGGCTATAG GTCTACTGGG TCAGGGGCTC GAGGACAGG CGGAGACACC CGCTATCCCA GTGCTAGTGG ACGGCACGGT CAGTCTTACA
*light chain start *CDR-L1

301 GAATCTGCT GTAGCTGGT ATCAACAGAA ACCAGGAAA GCTCCGAAGC TTCTGATTTA CTCGGCATCC TTCCTCTACT CTGGAGTCCC TTCTCGCTTC
CTTATGACGA CATCGGACCA TAGTTGTCTT TGTCTCTTTT CGAGGCTTCG AAGCTAAAT GAGCCGTAGG AAGGAGATGA GACCTCAGG AAGAGCGAAG
*CDR-L2

401 TCTGGTAGCC GTTCCGGGAC GGAITTTCACT CTGACCATCA GCAGTCTGCA GCCGGAAGAC TTCCCAACTT ATTACTGTCA GCAACATTTT ACTACTCTC
AGACCATCGG CAAGGCCCTG CCTAAGTGA GACTGTAGT GTCAGACGT CGGCTTCTG AAGCGTTGAA TAATGACAGT CGTTGTATAA TGATGAGGAG
*CDR-L3

501 CCAGGTTTCG ACAGGTACC AAGTGGAGA TCAACGAAC TGTGGCTGCA CCATCTGTCT GCATCTGAT GAGCAGTTGA AATCTGGAAC
GGTGCAAGCC TGTCCCATGG TTCCACCTCT AGTTGTGTTG ACACGACGT GGTAGACAGA AGTAGAAGGG CGGTAGACTA CTCGTCAACT TTAGACCTTG

601 TGCCTCTGTT GTGTGCTGTC TGAATAACTT CTATCCAGA GAGGCCAAG TACAGTGGAA GCGCTCCAAT CGGTAACCTC CCAGGAGGT
ACGGAGACAA CACACGGAGC ACTTATGAA GATAGGTCT CTCCGTTTC ATGTCACCTT CCACCTAATG CGGAGGTTA GCCATTGAG GGTCTCTCA

701 GTCACAGAGC AGGACAGCA GACAGCACC TACAGCCTCA GCAGCACCTT GACGCTGAGC AAGCAGACT ACGAGAAACA CAAAGTCTAC GCTCGGAAG
CAGTGTCTCG TCCTGTCTGT CCTGTCTGTG ATGTCGAGT GTCGCTGGA CTCGCACTCG TTTCGTCTGA TGCTCTTGT GTTTCAGATG CGGACGCTTC

801 TCACCCATCA GGGCTGAGC TCGCCCGTCA CAAAGAGCTT CAACAGGGA GAGTGTGGT CCAGTCCGG TATGGCTGAT CCGAACCGTT TCCGCGGTAA
AGTGGGTAGT CCGGACTCG AGCGGCGAGT GTTCTCGAA GTTGTCCCT CTCACACCAC GGTGAGGCC ATACCGACTA GGTGTGGCAA AGCGCCATTT

901 GACCTGGCA TAATCGAGG CTGATCTCT ACGCCGGAG CATCTGGCC CTATAGCGCA AGTTCACGTA AAAGGTTAA CTAGAGTTG AGGTGATTTT
CCTGGACCGT ATTGAGCTCC GACTAGGAGA TCGGCGCTGC GTAGCACCGG GATCATGGT TCAAGTGCAT TTTTCCCATT GATCTCCAAC TCCACTAAAA
*light chain stop

1001 ATGAAAAAGA ATATCGCAT TCTCTCTGCA TCTATGTTG TTTTCTAT TGCTACAAC GCGTACGCTG AGATCTCCA GGTTCAGCTG GTGGAGTCTG
TACTTTTCT TATAGCGTAA AGAAGAACGT AGATACAAGC AAAAAAGATA ACGATGTTG CGCATCGCAG TCTAGAGCT CCAAGTCGAC CACCTCAGAC
*start still secretion signal *heavy chain start

FIG. 16B

1101 GCGGTGGCT GGTGAGCCA GGGGCTCAC TCGTTTGT CTGTGAGCT TCTGCTTCA ACATTAAGA CACTATATA CACTGGTGC GTGAGGCC
CGCCACCGA CCAGTCGGT CCCCAGTG AGGCAACAG GACACGTGA AGACGAGT TGTAAITCT GTGATATAT GTGACCCAG CAGTCCGGG
*CDR-H1

1201 GGGTAAGGC CTGGAATGG TTGCAAGAT TTATCTAG ATGGTTATA CTAGATAGC CGATAGGTC AAGGCCGTT TCACTATAAG CGCAGACACA
CCCATTCCG GACCTTACCC AAGTTCCCTA AATAGATGC TTACCAATAT GATCTATAG GCTATGCGA TTCCGGGCAA AGTGATATTC CGGTCTGTGT
*CDR-H2

1301 TCCAAAACA CAGCTACCT ACAATGAAC AGCTTAAGAG CTGAGGACAC TGCCGTCTAT TANTGTAGCC GCTGGGGAGG GGACGGGTTT TATGCTATGG
AGGTTTTGT GTCCGATGA TGTITACTTG TCGAATCTC GACTCTGTG ACGGAGATA ATAACATCGG CGACCCCTCC CCTGCCGAAG ATACGATACC
*CDR-H3

1401 ACTACTGGG TCAAGGAACC CTGTACCG TCTCTCGG CTCCACCAAG GGCCTATCG TCTTCCCTT GGCACCTCC TCCAAGACA CCTCTGGGG
TGATGACCC AGTTCTCTGG GACCAGTGG AGAGAGCCG GAGGTGTTT CCGGTAGCC AGAAGGGGA CCGTGGGAGG AGGTCTCTGT GGAGACCC
*CDR-H4

1501 CACAGGGCC CTGGGCTGCC TGGTCAAGGA CTACTTCCC GAACCGTGA CGGTGCTGT GAACTAGGC GCCCTGACCA GCGGCGTGA CACCTTCCG
GTGTGCGCG GACCCGACG ACCAGTTCT GATGAAGGG CTGCGCACT GCCACAGAC CTTGAGTCCG CCGGACTGT CCGCGCACGT GTGGAAGGC
*CDR-H5

1601 GCTGTCTAC AGTCTCAG ACTCTACTCC CTCAGCAGG TGTGACCGT GCCCTCCAG AGCTTGGCA CCCAGACCTA CATCTGCAAC GTGAATACA
CGACAGATG TCAGGAGTCC TGAGATGAGG GAGTCTGCG ACCACTGCA CCGGAGTGT TCGAACCCGT GGTCTGGAT GTAGACGTTG CACTTAGTGT
*CDR-H6

1701 AGCCAGCAA CACCAAGTC GACAAGAA TTAGCCCAA ATCTTGTAC AAACTCAC CCAGTCCG TCGGTCTGT TCGGTGAT TTGATTATGA
TCGGTCTGT GTGGTCCAG CTGTCTTTC AACTCGGT TAGAACACTG TTTTGAAGTGG AGTCACCGCC ACCGAGACCA AGGCCACTAA AACTAATACT
*start p3 C-terminal domain

1801 AAAGATGCA AAGCTAATA AGGGGCTAT GACCGAAAAT GCGATGAAA ACGGCTACA GTCTGAGCT AAAGCAAC TTGATTCTGT CGCTACTGT
TTTCTACCG TTGCGATTAT TCCCGGATA CTGGCTTTT CCGCTACTTT TCGCGATGT CAGACTGCA TTTCGTTTG AACTAAGACA GCGATGACTA
*CDR-H7

1901 TACGGTCTG CTATCGATG TTTCAITGT GACGTTCCG GCCTTGCTAA TGGTAATGT GTTCTGCTG ATTTGCTGG CTCTAATCC CAAATGGTC
ATGCCAGAC GATAGCTACC AAGTAACCA CTGCAAGGC CGGAACGAT ACCATTACA CGATGACCAC TAAACGACC GAGATTAAAG GTTTACCGAG
*CDR-H8

2001 AAGTCGGTA CCGTGATAAT TCACCTTAA TGAATAATT CCGTCAATAT TTACCTTCC TCCTCAATC GGTGAATGT CGCCCTTTTG TCTTTAGCG
TTCAGCACT GCCACTATA AGTGAAAT ACTTATTA GGCAGTTATA AATGGAAGG AGGAGTTAG CCAACTTACA GCGGGAAC AGAATCGG
*CDR-H9

2101 TGGTAAACA TATGAATTT CTATTGATG TGACAAATA AACTTATCC GTGGTCTT TGGTCTCT TTATAGTTG CCACCTTAT GTATGTATT
ACCAITTTGT ATACTTAAA GATAACTAAC ACTGTTTAT TTGAATAGG CACCAGAA ACCGAAAGAA AATATACAAC GGTGGAATA CATACATAA
*CDR-H10

2201 TCTAGTTTG CTAACATACT GCGTAATAAG GAGTCTTAA
AGATGCAAC GATTGTATGA CGCATTAAT CTCAGAAAT
*end p3

FIG. 17A

1 GAATGAGCT GTTGACAATT AATCATCGGC TCGTATAATG TGTGGAATG TGAGCGGATA ACAATTTAC ACAGGAACA GCCAGTCCGT TTAGGTGTTT
CTTTACTCGA CAACGTGTAA TTAGTAGCGG AGCATATTAC ACACCTTAAC ACTCGCCTAT TGTAAAGTG TGTCTTTGT CGCTCAGSCA AATCCACAAA
*ptac promoter

101 TCACGAGCAC TTCACCAACA AGGACCATAG ATTATGAAAA TAAAAACAGG TGCACGCATC CTGCAATTAT CCGCATTAAC GACGATGATG TTTTCCGCCT
AGTGTCTGGT AAGTGGTGT TCCTGGTATC TAATACTTTT ATTTTGTCC AGTGGGTAG GAGCGTAATA GCGTAATTG CTGCTACTTAC AAAGCGCGA
*Start male secretion signal

201 CGGCTTATGC ATCCGATATC CAGATGACCC AGTCCCGAG CTCCTGTGCC GCCTCTGTGG CGCATAGGGT CACCATCACC TGCCGTGCCA GTACGATGT
GCCGAATACG TAGCTATAG GTCTACTGGG TCAGGGGCTC GAGGACAGG CGCTATCCCA GTGGTAGTGG ACGCACGGT CAGTCTTACA
*light chain start *CDR-L1

301 GAATACGCT GTAGCCTGGT ATCAACAGAA ACCAGGAAAA GCTCGAAGC TTCTGATTTA CTCGGCATCC TTCTCTACTI CTGGAGTCCC TTCTCGCTTC
CTTATGACGA CATCGGACCA TAGTTGTCTT TGGTCTTTT CGAGCCTCG AAGACTAAAT GAGCCGTAGG AAGGAGATGA GACCTCAGG AAGAGCGAAG
*CDR-L2

401 TCTGTAGCC GTTCCGGGAC GGAATTTACT CTGACCATCA GCAGTCTGCA GCCGGAAGAC TTCCGCAACT ATTACTGTCA GCAACATTAT ACTACTCTTC
AGACCATCGG CAAGGCCCTG CCTAAAGTGA GACTGGTAGT CGTCAGACGT CGGCTTCTG AAGCTTGAA TAATGACAGT CGTTGTAATA TGATGAGGAG
*CDR-L3

501 CCACGTTCCG ACAGGTACC AAGTGGAGA TCAACGAAC TGTGCTGCA CCATCTGTCT TCATCTTCCC GCATCTGAT GAGCAGTTGA AATCTGGAAC
GGTGAAGCC TGTCCCATGG TTCCACCTCT AGTTTGTCTG ACACGACGT GGTAGACAGA AGTAGAAGGG CGGTAGACTA CTCGTCAACT TTAGACCTTG

601 TGCTCTGTT GTGTGCTGC TGAATTAATT CTATCCGAGA GAGGCCAAG TACAGTGGAA GGTGATTAAC GCCCTCCAAT CGGTAACCTC CCAGGAGAGT
ACGGAGACAA CACAGGAGC ACTTATTGAA GATAGGCTCT CTCGGTTTC ATGTCACTT CCACCTATTG CGGAGGTTA GCCCATTCAG GGTCTCTTCA

701 GTACACAGC AGGACAGCAA GGACAGCAC TACAGCCTCA GCAGCACCTT GACGCTGAGC AAAGCAGACT ACAGAAACA CAAAGTCTAC GCCTGCGAAG
CAGTGTCTCG TCCTGTCTGT CCGTGTCTGT ATGTGGAGT CGTGTGGGA CTGCGACTCG TTTCTCTGA TGTCTTTGT GTTTCAGATG CGGACCGCTC

801 TCACCCATCA GGGCTGAGC TCGCCGCTCA CAAGAGCTT CAACAGGGA GAGTGTGCTG CCAGTCCGG TATGGTGTAT CCGAACCGTT TCCGCGGTAA
AGTGGTAGT CCGGACTCG ACGGGCAGT GTTCTCGAA GTTGTCCCT CTCACACAC GGTGAGGCC ATACCGACTA GGTCTGGCAA AGCGGCCAAT

901 GGACCTGGCA TAATCTGAG CTGATCTCT ACGCGGAGC CATCTGGCC CTAGTACGCA AGTTCACTGA AAAGGGTAA CTAGAGGTTG AGTGATTTT
CCTGGACCGT ATTGAGCTCC GACTAGGAGA TCGGCGCTGC GTAGCACCGG GATCATGCGT TCAAGTGAT TTTTCCCAT TATCTCCAAC TCCACTAAAA
*light chain stop

1001 ATGAAAAAGA ATATCGCAT TCTTCTTGCA TCTATGTTGG TTTTCTAT TGTACAAC GGTAGGCTG AGATCTCGA GGTTCAGCTG GTGAGTCTG
TACTTTTCT TATAGCGTAA AGAAGACGT AGATACAAGC AAAAAAGATA ACGATGTTG CGCATCGGAC TCTAGAGGCT CCAAGTCGAC CACCTCAGAC
*start stII secretion signal *heavy chain start

FIG. 17B

1101 GCGTGGCT GTGCGAGCA GGGGGCTCAC TCGGTTGTC CTGTGAGCT TCGTGCTTCA ACATTAAGA CACCTATATA CACTGGTGC GTACGGCCCC
GCCACCGGA CCACGTGGT CCCCCAGTG AGGCAACAG GACACGTGA [^]CDR-H1 GTGATATAT GTGACCCAG CAGTCCGGGG

1201 GGGTAAGGC CTGGAATGG TTGCAAGAT TTATCTACG AATGGTATA CTAGATAGC CGATAGGTC AAGGCCGTT TCACTATAA GCGACACACA
CCCATTCGG GACCTTACCC AACGTTCTTA AATAGGATGC TTACCAATAT GATCTATAG GCTATCGAG TTCCCGGCAA AGTGATATTC GCGTCTGTGT
[^]CDR-H2

1301 TCCAAAAACA CAGCCTACCT ACAATGAAC AGCTTAAGAG CTGAGGACAC TGCCGTCTAT TATTGTAGC GCTGGGAGG GGACGGCTTC TATGCTATGG
AGGTTTTGT GTCGGATGA TGTTTACTTG TCGAATCTC GACTCCTGT AGGGGAGATA ATACATCGG CGACCCCTCC CCTGCCGAAG ATACGATACC
[^]CDR-H3

1401 ACTACTGGG TCAAGGAACC CTGCTCACCG TCTCTCGGC CTCACCAAG GCGCCATCGG TCTTCCCTCC TCCAAGAGCA CCTCTGGGG
TGATGACCCC AGTTCTTTGG GACCAGTGGC AGAGGAGCCG GAGGTGTTT CCGGGTAGCC AGAAGGGGA CCGTGGGAG AGGTCTCGT GGAGACCCCC

1501 CACAGCGGC CTGGGCTGCC TGGTCAAGGA CTACTTCCC GAACGGTGA CGGTGTGTC GAACTCAGC GGCCTGACCA CGGCGTGCA CACCTTCCCG
GTGTCGCCG GACCCGAGG ACCAGTTCT GATGAAGGG CTTGGCCACT GCCACAGCAC CTTGAGTCG CGGACTGGT CGCGCACGT GTGGAAGGGC

1601 GTGTCTTAC AGTCTCAGG ACTCTACTCC CTCAGCAGCG TGGTGACCTT GCGCTCCAGC AGCTTGGGA CCGAGACCTA CATCTGCAAC GTGAATCACA
CGACAGATG TCAGAGTCC TGAGATGAG GAGTGTGCG ACCACTGGCA CCGGAGGTG TCGARCCGT GGGTCTGGAT GTAGACGTTG CACTTAGTGT

1701 AGCCAGCAA CACCAAGTC GACAGAAAG TTGAGCCAA ATCTGTGAC AAAAACTACA CATGCCCGC GTGCCAGCA CCAGAACTGC TGGCGGCCG
GTGGTCCAG CTGTTCTTC AACTCGGTT TAGAACATG TTTGAGTGT GTACGGCGG CACGGTGT GGTCTGACG ACCCGCCCG
[^]start zipper

1801 CATGAACAG CTAGAGACA AGGTGAAGA GCTACTCTCC AAGAACTACC ACCTAGAA TGAAGTGGCA AGACTCAAA AACTGTGCG GGAGCGCGA
GTACTTTGTC GATCTCTGT TCCAGCTTCT CGATGAGG TTCITGATG TGGATCTCTT ACTTCACCGT TCTGAGTTT TTGAACAGCC CCTCGCCCT

1901 AAGCTTAGT GCGGTGGCTC TGGTTCGGT GATTTGANT ATGAAGAAT GGCAACGCT AATAAGGGG CTATGACCGA AATGCCGAT GAAAAAGCGC
TTGCAATCAC CGCCACCGAG ACCAAGCCA CTAAAACTAA TACTTTTCTA CCGTTTGGGA TTAITCCCC GATACTGGCT TTTAGGGCTA CTTTGGCGG
[^]start p3 C-terminal domain

2001 TACAGTCTGA CGCTAAAGC AAACITGANT CTGTGCTAC TGATACGGT CTTGCTATCG ATGTTTTCAT TGGTAGGTT TCCGGCCTTG CTAATGGTAA
ATGTCAGACT GCGATTTCCG TTGAACTAA GACAGCATG ACTAATGCCA CGAGGATAGC TACCAAGTA ACCACTGCAA AGCCCGAAC GATTACCAT

2101 TGGTGTACT GGTGATTTG CTGGCTCTAA TTCCCAAATG GCTCAAGTC GTGACGGTGA TAAITCACCT TTAATGAATA ATTTCCGTCA ATATTACCT
ACCAAGATGA CCACTAAAAA GACCGAGTT AAGGTTTAC CGAGTTTAC CACTGCCACT ATTAAGTGA AATTACTTAT TAAAGCAGT TATAAATGGA

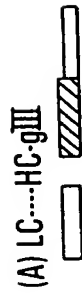
2201 TCCCTCCCTC AATCGTTGA ATGTGCCCCT TTTGTCTTAA GCGCTGGTAA ACCATATGAA TTTTCTATTG ATTGTAGCAA AATAAACTTA TTCGTGGTG
AGGAGGGAG TTAGCCAAT TACAGCGGA AACAGAAAT CCGGACCAIT TGGTATACTT AAAAGATAAC TAACTAGT TTAATTGAAT AAGGCACCAC

2301 TCTTTGCGTT TCTTTTAT TATGCTACCT TTATGATGT ATTTCTACG TTTGCTAACA TACTGGTAA TAAGGAGTCT TAA
AGAAACGCAA AGAAATATA CAACGGTGA AATACATGA TAAAGATGC AAACGATTGT ATGACCAIT ATTCTCAGA ATT
[^]end p3

Fig. 18

F(ab) OR F(ab)' 2-PHAGE

(A) LC---HC-gIII



(B) LC---HCZIP(AMBER)-gIII



(C) LC---HCZIP-gIII

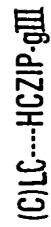
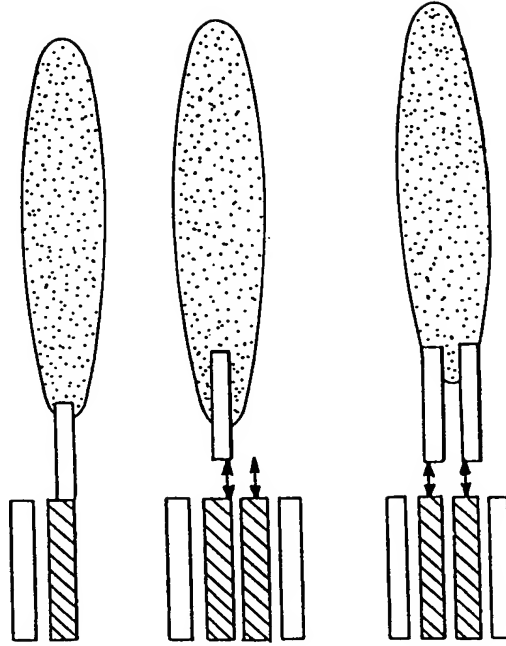



Fig.19

IN SOLUTION BINDING ASSAY, ZIPPED (Fab')₂ PHAGE
BINDS WITH SIMILAR AFFINITY AS Fab-PHAGE

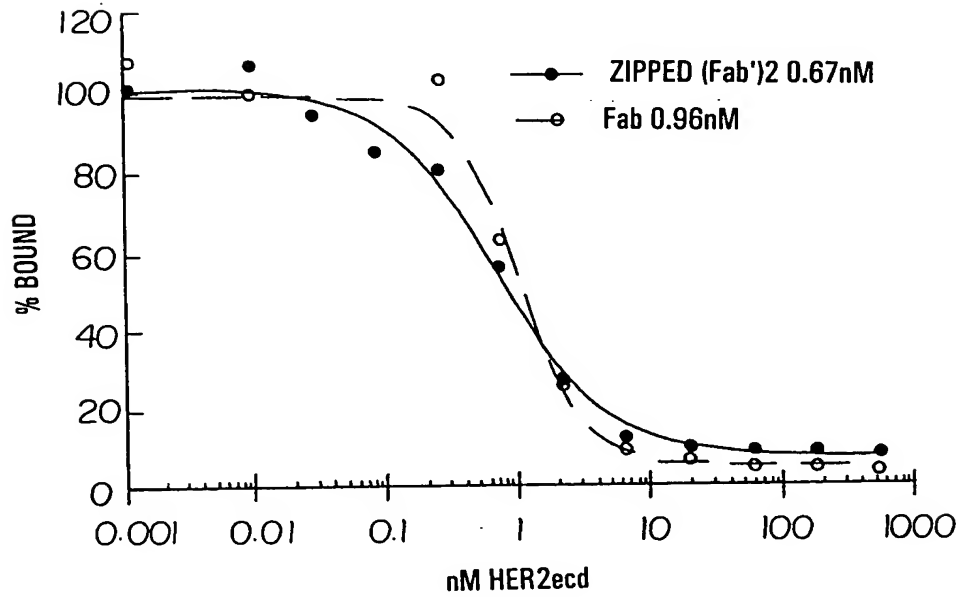


Fig.20

**SLOW OFF-RATE OF ZIPPED Fab
INDICATES THE FORMATION OF (Fab')₂ ON PHAGE**

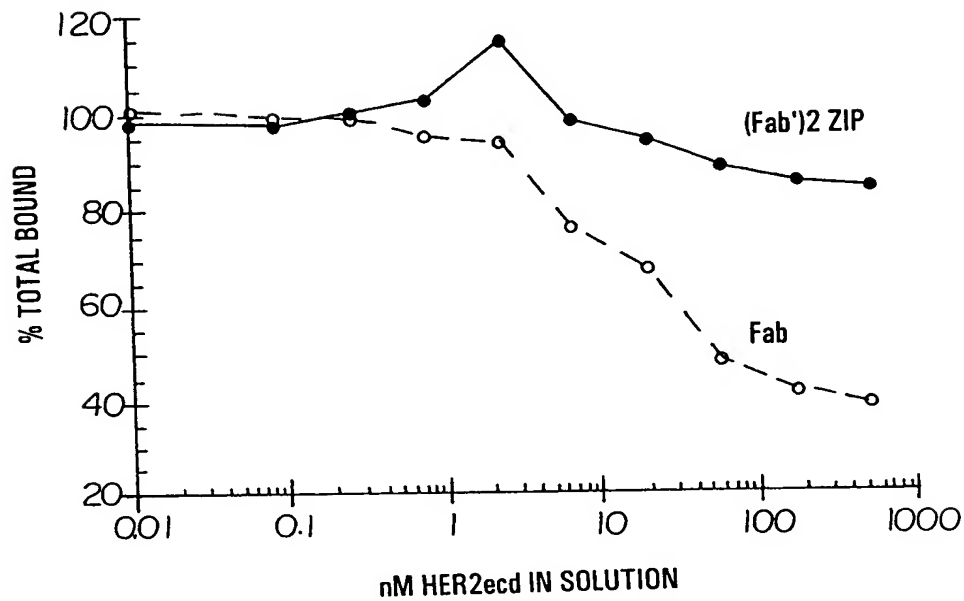


Fig.21

HERCEPTIN WT (0.2nM) BINDING TO HER2ecd

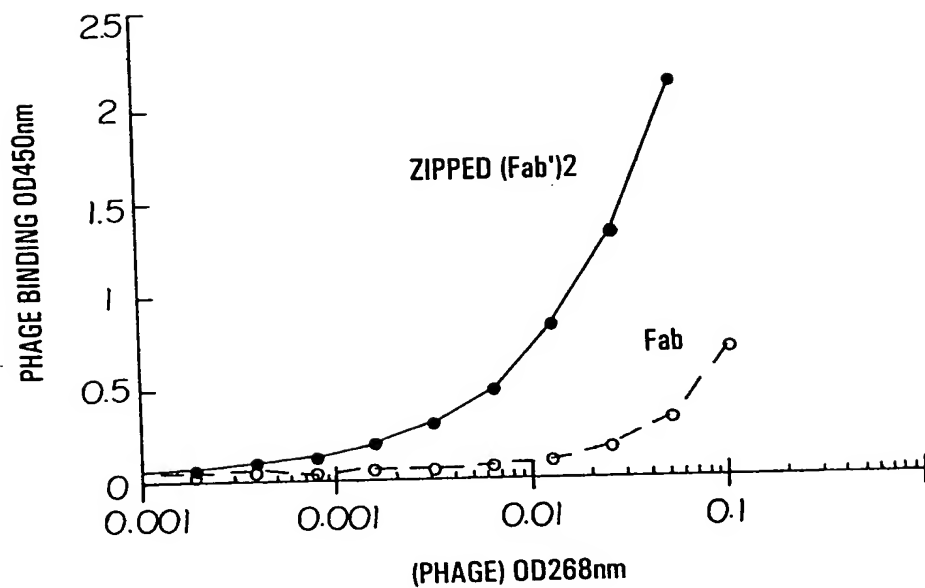


Fig.22

HERCEPTIN (HC/R50A,610nM)
BINDING TO HER2ecd

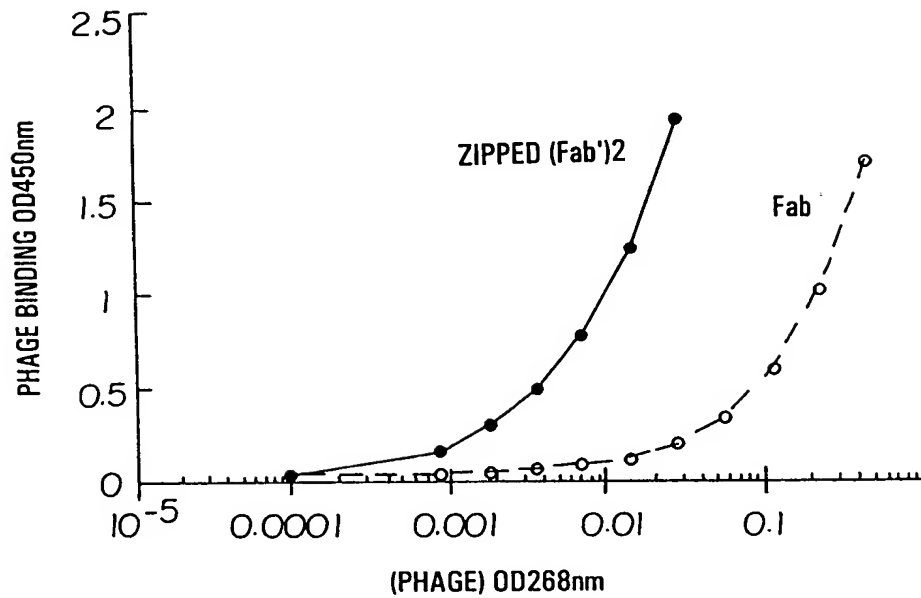
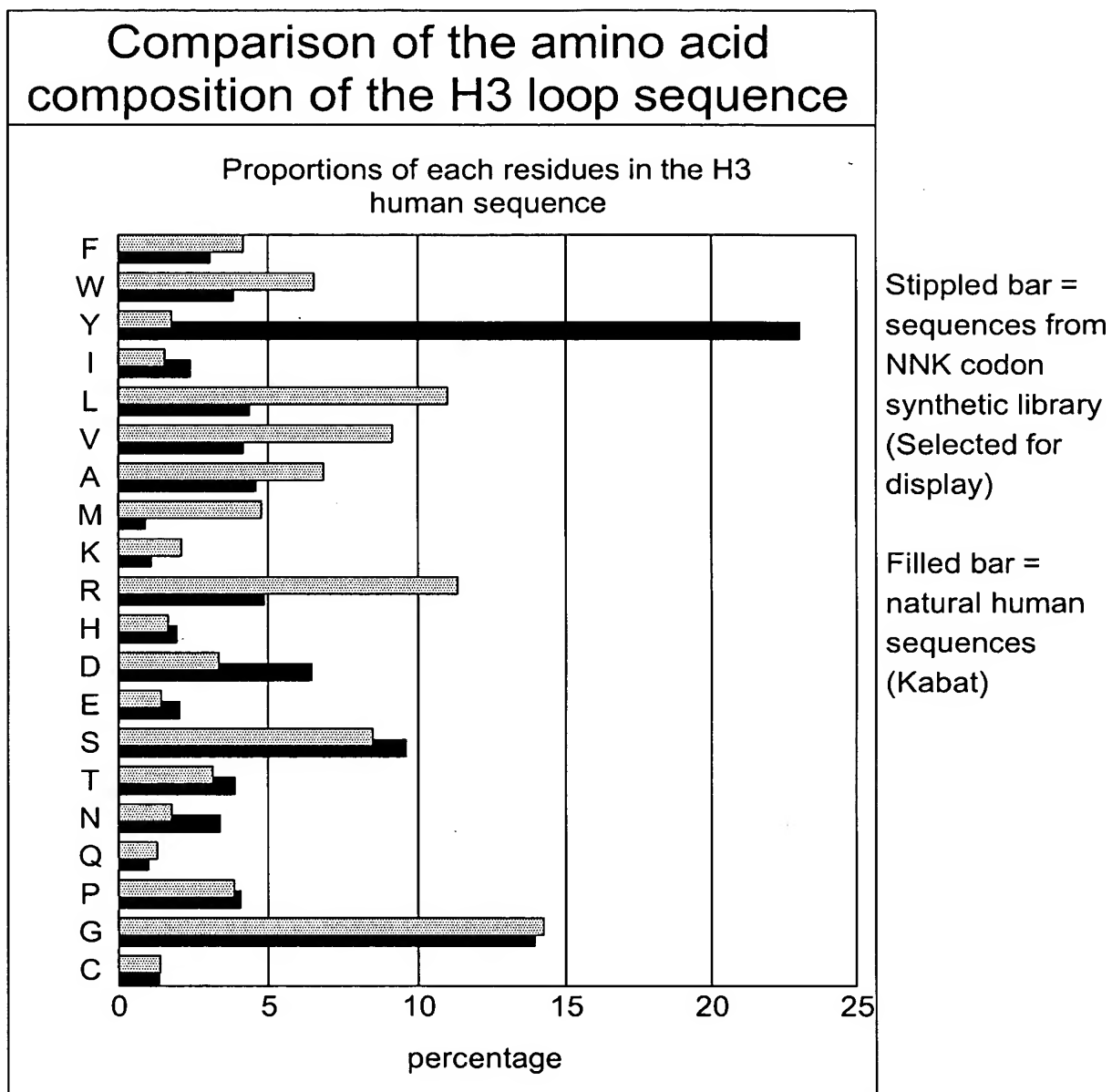


FIG.23



Aliphatic hydrophobic residues occur more frequently in NNK synthetic library than in natural sequences.

FIG. 24

CDR-H1:

28	30	31	32	33
AVT	RVM	RVM	WMY	KVK
N	A2	A2	N	A2
S	D	D	S	C
T	E	E	T	D
	G2	G2	Y	E
	K	K		G2
	N	N		S2
	R	R		Y
	S	S		W
	T2	T2		*

CDR-H2:

50	52	53	54	56	58
KDK	DMT	NMY	DMK	DMK	DMT
C	A	A	A2	A2	A
D	D	D	D	D	D
E	N	H	E	E	N
F	S	N	K	K	S
G2	T	P	N	N	T
L	Y	S	S2	S2	Y
V2		T	T2	T2	
W		Y	Y	Y	
Y			*	*	
*					

*Amber (TAG) stop codon is encoded by the degenerate codon

CDR-H3:

6-8 "DVK" codons (18) encoding
12 amino acids (ACDEGKNRSTYW) and stop (*)

FIG. 25
ScFv Library Sorting Results

Library	Binders		
	Her2	IGF	VEGF
scFv-1 (H1/H2/H3)Zip	100%	100%	63%
ScFv-2 (L3 /H1/H2/H3)Zip	50%	63%	25%
scFv-3 (L3/H3)Zip	88%	88%	88%
scFv-4 (H1/H2/H3)	38%	50%	63%
scFv-5 (L3 /H1/H2/H3)	25%	13%	25%

FIG. 26
Detailed Analysis of scFv Zipper Libraries

Binding clones

Library	IGF		VEGF	
	Total	Specific	Total	Specific
scFv-1	91%	67%	79%	70%
scFv-2	84%	54%	52%	22%
scFv-3	88%	8%	91%	4%

FIG. 27 **Summary of Sequencing Results**

Library	Round	Sequences	
		Total	Unique
anti-IGF			
scFv-1	2	72	65
scFv-1	3	95	79
scFv-4	3	88	48
Sum		255	192
anti-VEGF			
scFv-1	2	24	22
scFv-1	3	87	45
scFv-4	3	91	19
Sum		202	86

FIG. 28

Table X
CDR-H3 Usage in Binding Clones

	95	96	97	98	99	100	100a
4D5	W	G	G	D	G	F	Y
F59	W	G	X	X	X	X	X
F63	X	X	X	X	X	X	X
F64	X	X	X	X	X	X	Y
F65	X	X	X	X	X	X	Y

Percentage of each CDR-H3 in binders

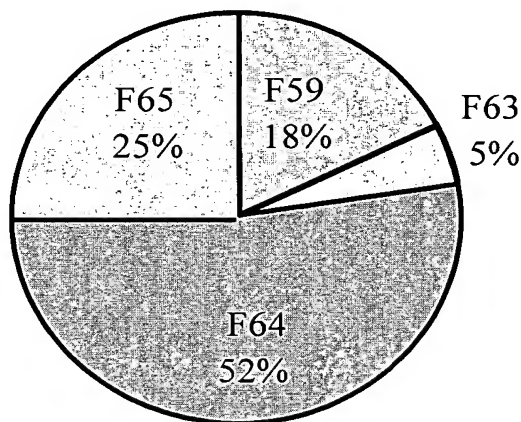


FIG. 29
Binders from L3/H3 library, sort 2
(1-4% hit rate)

H3 Sequences of IGF1 binders (3/8)				
	Sequences	# clones	Source Oligo	IC50 (uM)
I1	<u>SR</u> WKYATR <u>YAM</u>	1	(DVK)5(NNK)1	40
I2	<u>SR</u> SRGWWT <u>AAM</u>	1	(DVK)7	0.3
I3	<u>SR</u> ASRDWYG <u>AM</u>	1	(DVK)7	15
H3 sequences of mVEGF binders (10/25)				
V1	<u>SR</u> NAWA <u>F</u>	6	(DVK)5	5.0
V2	<u>SR</u> NLSNS <u>YAM</u>	1	(NNK)6	0.2
V5	<u>SR</u> AGWAGW <u>YAM</u>	1	(DVK)5(NNK)1	0.6
V8	<u>SR</u> AAKAGW <u>YAM</u>	1	(DVK)5(NNK)1	4.7
V10	<u>SR</u> SDGRDSA <u>YAM</u>	1	(DVK)6(NNK)1	6.0

Fig.30

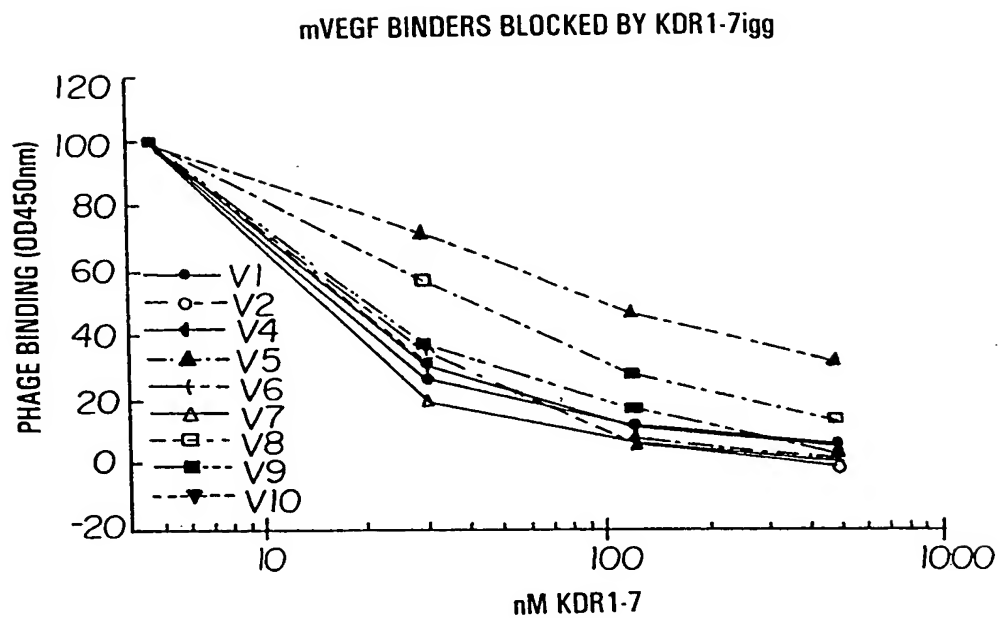


Fig.31

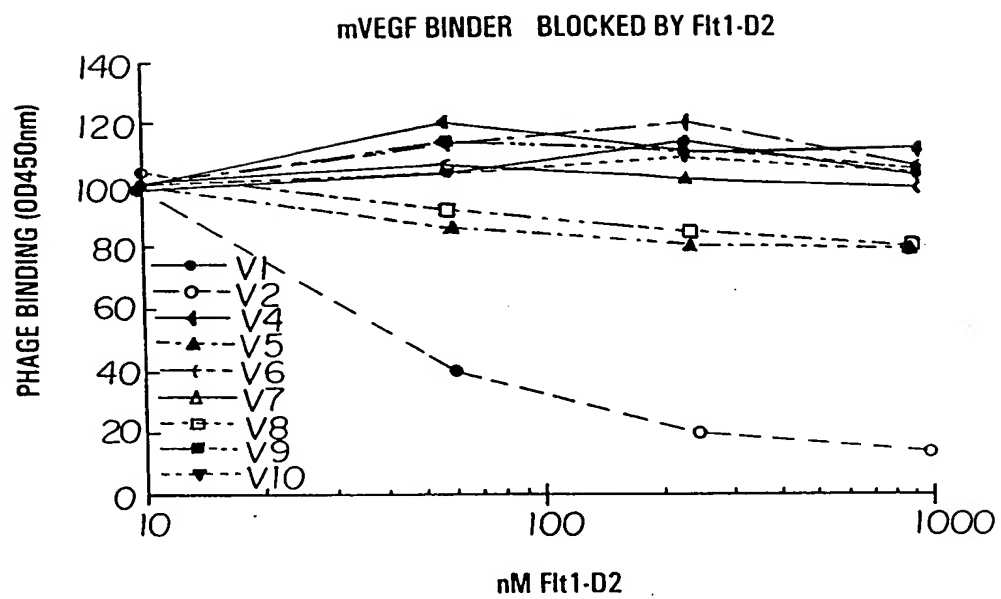


FIG. 32

Further Characterization of the mVEGF binders

	H3 seq	IC50 (uM)	Blocking reagent			Fab Protein
			Flt-D2	KDR	Y317	
V1	SRNAWA F	5.0	-	+	+	-
V2	SR NLSNS YAM	0.2	+	+	+	+
V5	SR AGWAW YAM	0.6	-	+/-	+/-	+
V8	SR AAKAGW YAM	4.7	-	+/-	+/-	+

FIG. 33

mVEGF-201	28	30	31	32	33	49	50	52	53	54	56	58	71	93	94	95	96	97	98	99	100	100a	Affinity	
	T	T	S	N	G	A	Y	S	S	N	Y	Y	R	A	R	W	S	R	A	S	F	Y	>5uM	
	T	T	G	T	D	A	I	T	Y	D	S	Y	R	A	K	A	G	D	R	E	G	Y	200nM	
	T	T	D	S	G	G	R	S	Y	S	S	N	R	A	K	W	P	W	Y	N	A	W	700nM	
hFc-10	28	30	31	32	33	49	50	52	53	54	56	58	71	93	94	95	96	97	98	99	100	100a	Affinity	
	T	N	N	Y	W	G	Y	S	S	Y	G	T	R	A	K	A	X	K	G	S	L	Y	2uM	
	T	T	G	N	A																	>1uM		
	T	N	D	Y	Y																			
hFc-11	T	N	D	Y	Y																			
hFc-12	T	N	D	Y	Y																			
hFc-13	T	S	N	T	G																			
hFc-14	T	T	S	Y	G	A	S	S	S	Y	S	Y	R	A	K	Y	X	A	R	E	G	X		
hFc-15	T	N	N	N	S	G	Y	N	S	S	G	S	R	A	K	W	R	T	S	W	K	Y		
hFc-16	T	S	S	S	A	A	W	S	S	N	G	S	R	A	X	T	A	G	G	A	K	Y		
hFc-17	T	T	N	T	W	G	D	Y	Y	D	G	Y	R	A	X	W	R	W	G	R	Y			
hFc-18	T	N	G	N	Y	G	W	S	S	N	G	Y	R	A	R	Y	S	G	G	R	Y	40nM		
hFc-19	T	S	N	N	A	G	R	S	S	Y	N	Y	R	A	X	G	X	T	S	G	G	Y		
hFc-20	T	T	S	N	D	A	W	S	S	Y	N	Y	R	A	R	R	S	R	W	S	R	A		
hFc2	(sequence not determined)																							~2uM

(sequence not determined)

FIG. 34A **Phagemid construct**

A. Vector for Fab-pIII display

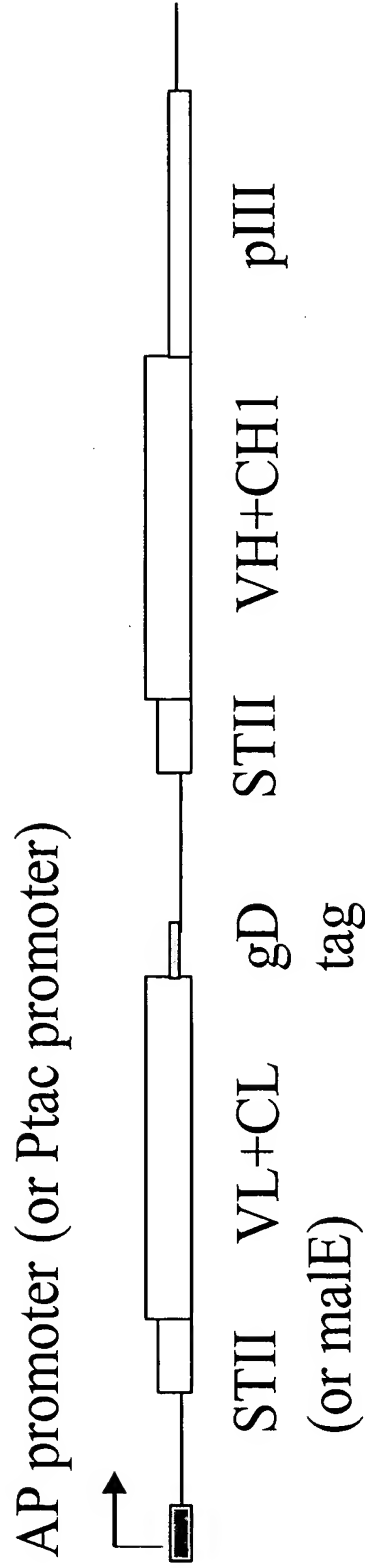


FIG. 34B B. Vector for Fab'2-pIII display

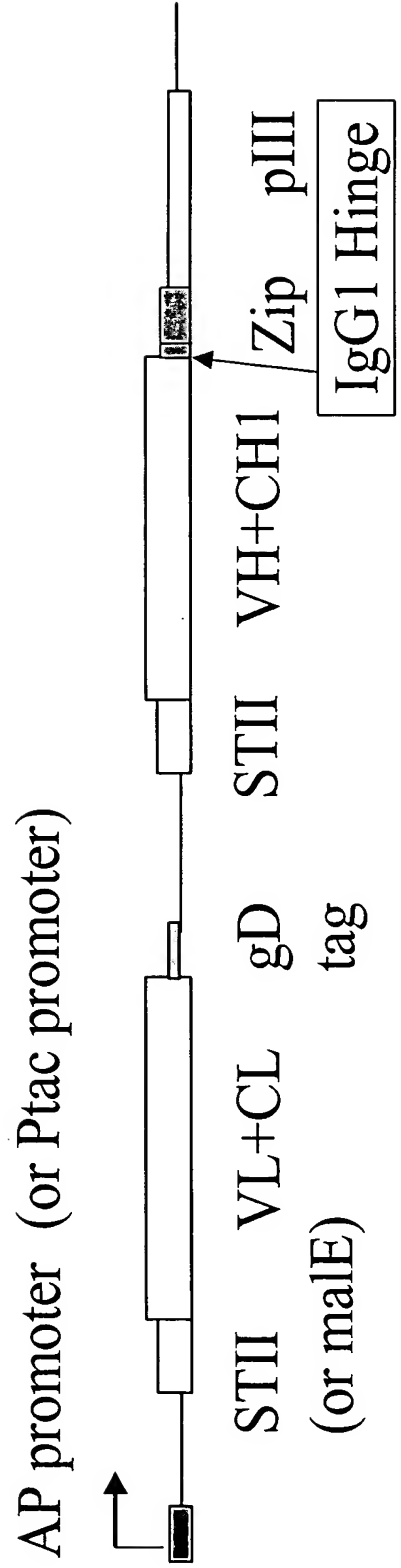


FIG. 34C

C. Vector for $\text{ScF}_V\text{-pIII}$
AP promoter (or Ptac promoter)

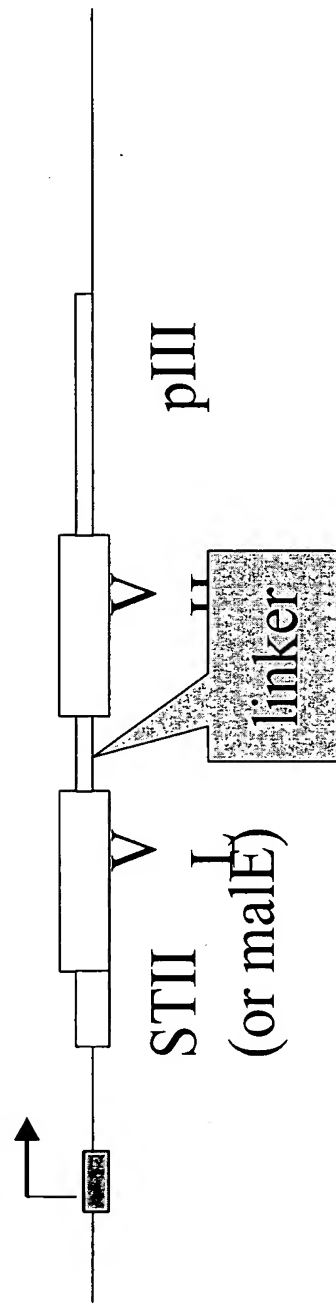


FIG. 34D

D. Vector for $(\text{ScF}_V)_2\text{-pIII}$
AP promoter (or Ptac promoter)

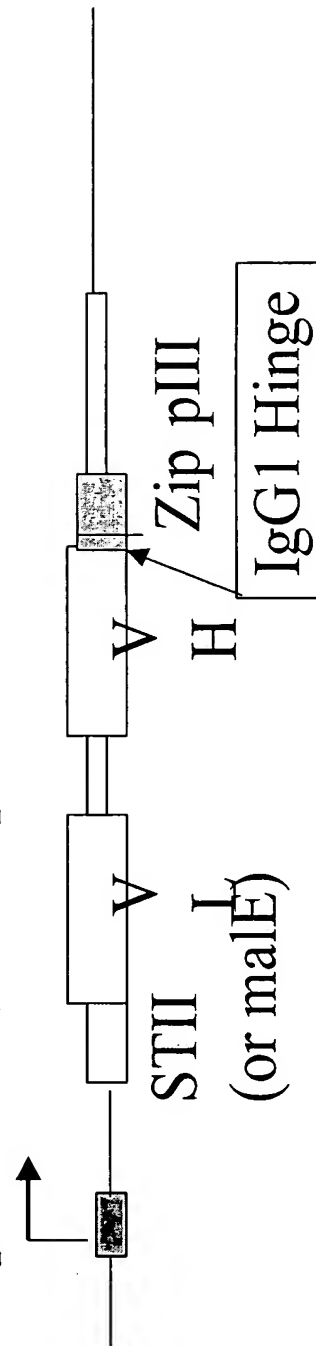


FIG. 35

	28	30	31	32	33	50	52	53	54	56	58	95	96	97	98	99	100	100a	Affinity uM
mVEGF-109	T	G	N	S	W	V	A	T	Y	Y	N	W	G	A	K	G	T	W	0.13
mVEGF-126	N	A	D	S	A	Y	A	Y	D	Y	Y	W	G	W	T	T	N	G	0.58
mVEGF-127	N	D	N	T	A	V	S	H	D	T	Y	W	G	W	E	T	D	G	0.83
mVEGF-130	N	A	D	S	A	L	D	S	S	Y	D	S	R	A	G	Y	T	Y	0.2
mVEGF-136	N	G	K	S	S	W	S	Y	E	A	A	T	S	W	S	K	P	Y	0.45
mVEGF-169	N	T	A	Y	G	V	T	Y	D	D	T	W	G	W	E	A	N	W	0.15
mVEGF-173	T	G	G	S	W	V	Y	T	Y	Y	D	W	G	A	G	G	T	W	0.27
mVEGF-174	T	G	G	S	W	V	S	D	Y	Y	D	W	G	S	G	Y	T	W	0.13
mVEGF-176	S	A	G	Y	D	L	A	Y	A	Y	N	A	A	A	W	A	S	Y	0.7
mVEGF-179	T	T	E	S	G	V	Y	H	D	K	Y	W	W	Y	S	W	N	W	0.13

FIG. 36

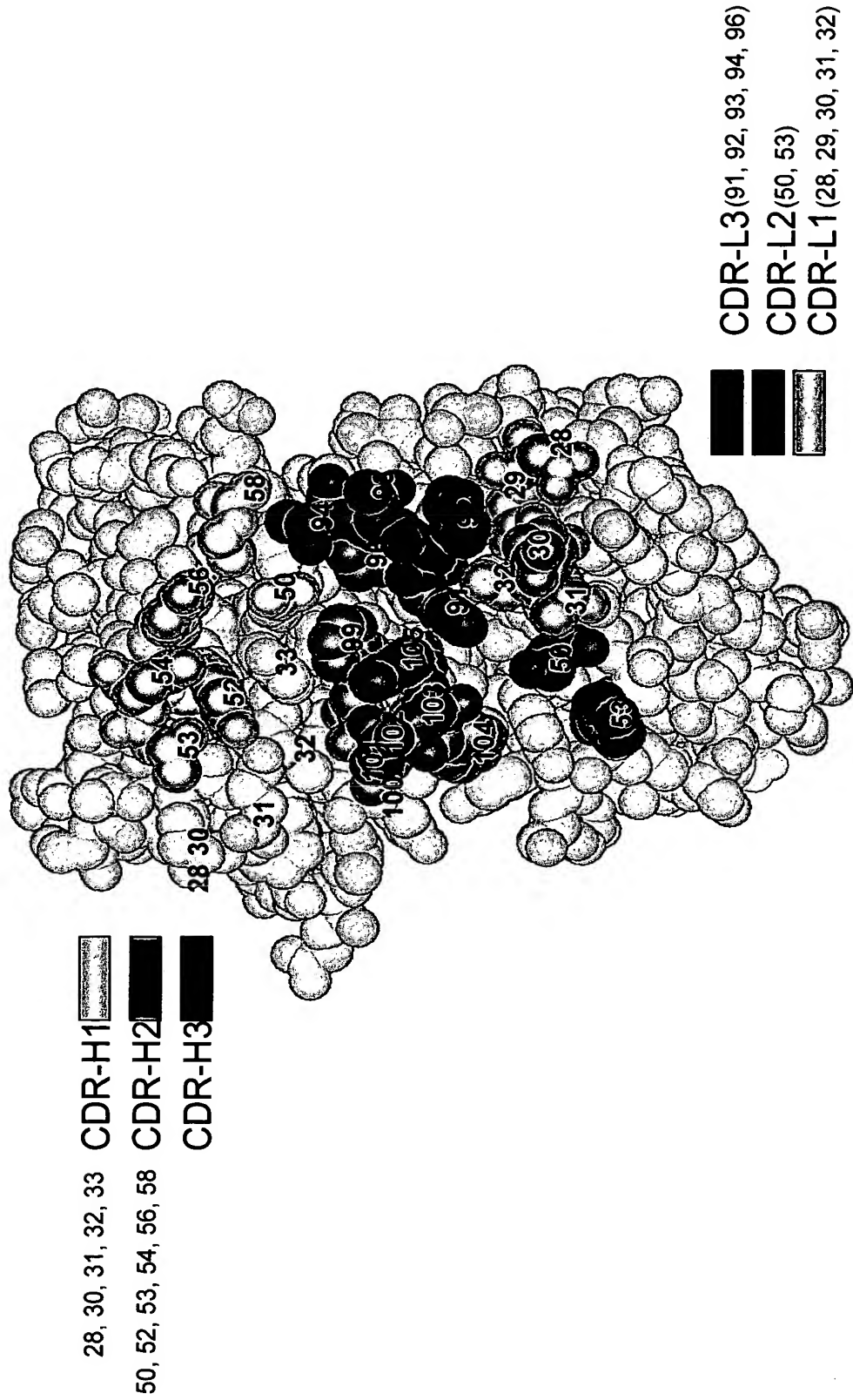


FIG.37

```

GAT GTT CAG TTG CAG GAA TCA GGC GGT GGC TTG GTA CAG GCC GGA 45
GGT TCG TTG CGT TTG TOC TGT GCT GCC TCG GGT OGT ACT GGT TCT 90
ACT TAT GAT ATG GGC TGG TTT CGT CAG GCT OCG GGT AAA GAA CGT 135
GAA TCG GTT GGC GGC ATT AAC TGG GAT TCG GCT OGT ACT TAC TAT 180
GCT TCG TCC GTC OGT GGT CGT TTT ACT ATT TCA OGT GAT AAT GGC 225
AAA AAA ACT GTC TAT TTG CAG ATG AAT TCA TTG AAA CCA GAA GAT 270
ACT GCC GTC TAT ACT TGT GGT GCT GGT GAA GGC GGT ACT TGG GAT 315
TCT TGG GGT CAG GGT ACC CAG GTC ACT GTC TOC TCT GGC GGT GGT 360
ATG GAT TAT AAA GAT GAT GAT GAT AAA TGA 390

```

a.)

```

DVQLQ ESGGG LVQAG GSLRL SCAAS GRTGS TYDMG WFRQA PGKER ESVAE
      5      10      15      20      25      30      35      40      45      50

```

```

INWDS ARTYY ASSVR GRFTI SRDNA KKTVE LQMNS LKPED TAVYT CGAGE
      54      59      64      69      74      79      82b     86      91      96

```

```

GGTWD SWGQG TQVTV SSAGG MDYKD DDDK
      101      106      111      116      121      126

```

b.)

```

C G A G X X X X X X X X X X X X X X X X W G
92 93 94 95 96 97 98 99 100 100a 100b 100c 100d 100e 100f 100g 100h 100i 100j 101 102 103 104

```

c.)

Nucleotide (a.) and amino acid sequence (b.) of the Llama anti-HCG parent scaffold. The numbering system for the 17 Residue CDR3 loop is shown in (c.)

Wild Type CDR3 Alanine Scan

FIG.38

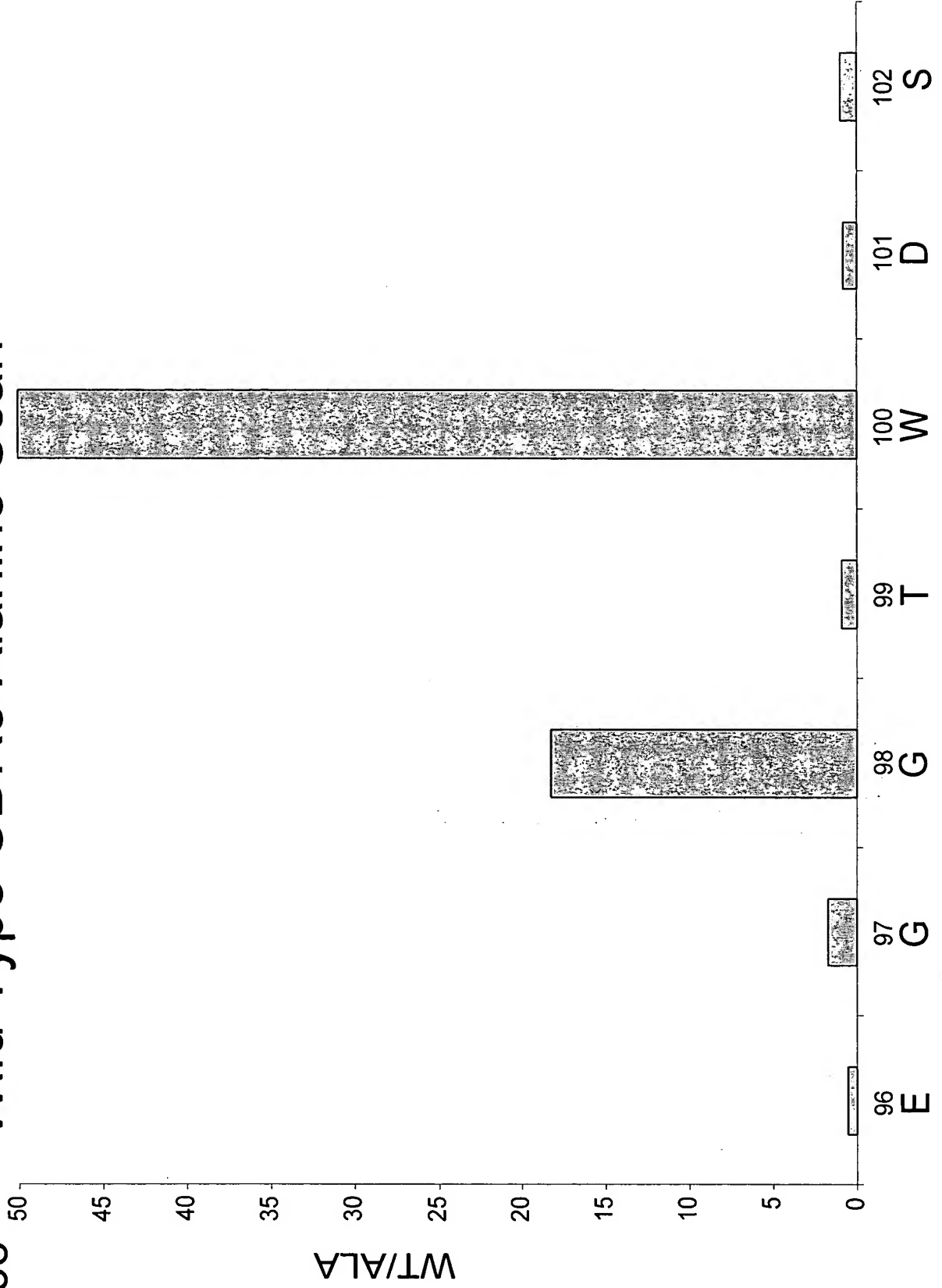
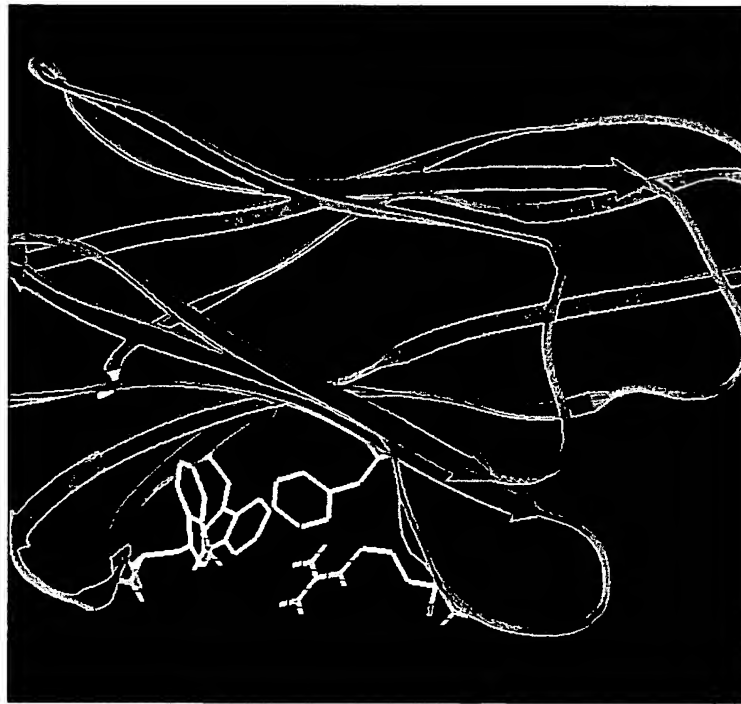
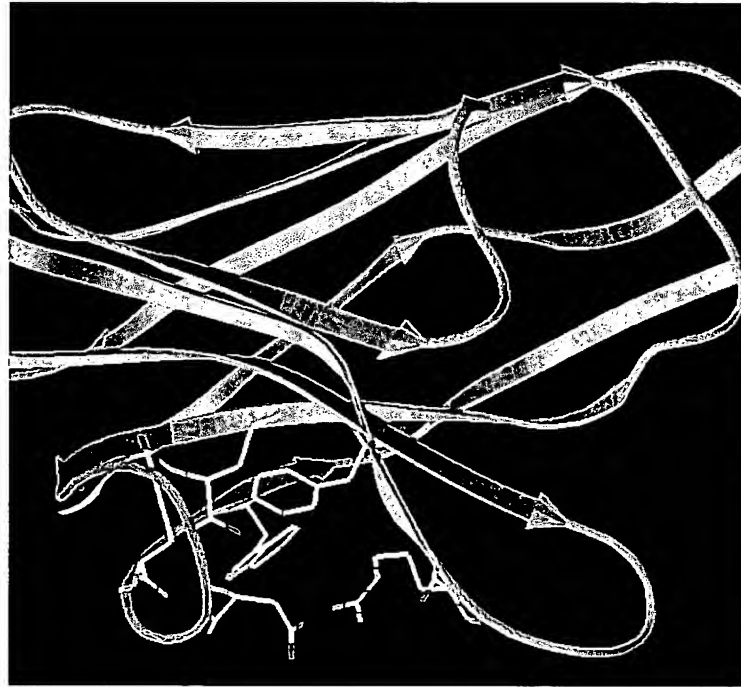


FIG. 39

Interface Packing by CDR3



α -HCG



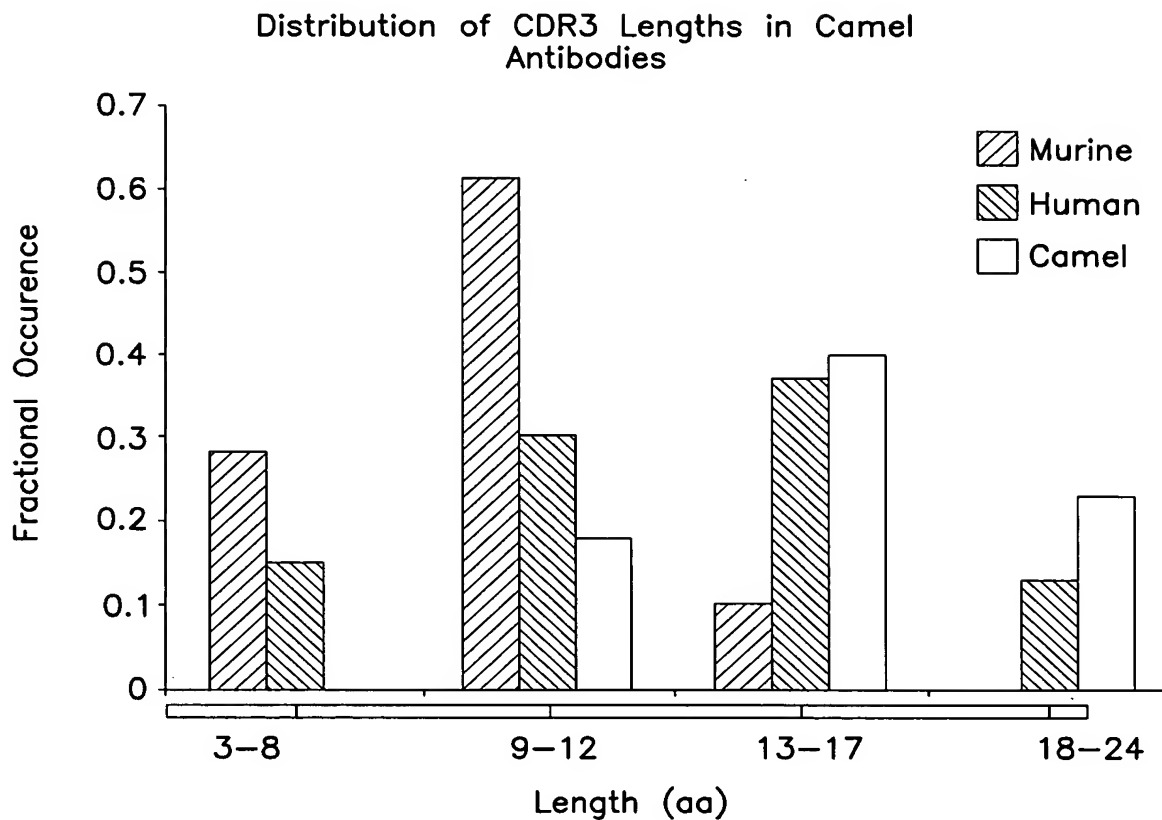
α -RNase A

FIG.40

Amino Acid Bias in VhH Framework

Residue	WT	Codon	C	A	V	L	I	P	F	Y	W	M	G	S	T	N	Q	D	E	K	R	H
37	Phe	NNS		2.8	2.1	0.4			65.8	1.4	21		0.7	0.4					1.4	1.4	0.9	
45	Arg	NNS		1.4	4.4	7.9		4.4		2.9	2.9	8.9	2.9	2.9	1.4		2.9			2.9	47.5	5.9
47	Ser	NNS		6.7	1.1	6.7	2.2	1.1	6.7		29.2	4.4		22.4	3.3		4.4	4.4	4.4		2.2	
91	Thr	NNS		1.9	5.7	14.1	3.8		40.5	9.6	5.7	3.8	0.9	1.2	1.9			3.8		1.9	4.5	

FIG.41



CDR3 in dromedary ad's is longer reflecting dual role

FIG.42 Amino Acid Bias in CDR3

Position	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
96	2	3	1	5	29	1	10	7	13	18	5		3	6	35	6	6	16	11	11
97	3	6			19	6	1	28		52	19		2		8	4	1	15	12	6
98	10	2	3	14	15	15	1	7	15	13	15	3	3	8	20	12	7	14	19	1
99	9	1	7	9	12	13	1	2	10	7	9	11	10	7	32	8	4	8	19	10
100	12	2	16	3	13	24	4	6	7	6	7	3	12	4	18	18	5	8	17	3
100a	8	2	6	10	11	25	2	6	2	10	6	1	12	7	17	10	3	21	26	6
100b	9	4	4	5	26	27	5	6	5	8	1	19	8	4	9	16	5	10	31	4
100c	13	2	5	4	18	33	4	4	11	8	5	17	8	14	10	12	3	4	35	3
100d	11	1	3	12	11	29	5	3	9	18	6	4	6	7	12	8	11	7	25	3
100e	12	3	5	11	15	17	4	2	4	12	6	8	17	6	13	9	5	15	25	5
100f	11	3	8	8	14	12	4	8	3	10	7	13	11	4	16	8	3	15	41	5
100g	10		6	22	35	13	4	2	5	9	13	3	8	2	12	5	11	10	49	4
100h	4	1	4	17	56	9	5	3	3	17	8	1	7	2	9	13	7	3	39	6
100i	9	4	3	7	4	12	3	5	17	8	20	4	5	11	19	10	8	9	40	10
100j	10	2	2	7	8	8		12		13	5	2	27	7	4	7	6	40	23	
101	10	2	2	8	6	6	8	3	11	18	17		3	17	8	8	13	24	31	6
102	22	2	2	2	21	10	3	27	4	4	7	2		9	5	16	6	26	28	14

FIG.43

a

Residue	C	A	V	L	I	P	F	Y	W	M	G	S	T	N	Q	D	E	K	R	H	Total	Frequency
96	2	2	14	16	6	3	23	10	11	5	1	5	5	0	5	1	4	12	32	10	166	0.05
97	4	3	13	47	25	2	16	5	10	17	6	3	1	0	0	0	0	0	7	1	159	0.05
98	1	10	13	10	6	3	14	1	18	14	14	10	5	3	7	3	13	15	18	1	177	0.05
99	1	9	8	7	2	9	12	8	13	9	11	7	3	11	6	6	8	10	30	1	170	0.05
100	2	12	6	6	6	11	13	3	14	7	21	16	5	2	4	14	3	7	15	4	169	0.05
100a	1	7	19	9	6	10	10	4	24	5	23	10	3	1	7	6	8	1	16	1	168	0.05
100b	4	9	10	7	6	6	23	4	29	0	23	15	5	16	3	3	4	5	9	5	184	0.05
100c	2	12	2	7	3	8	17	3	32	4	29	10	3	16	14	4	4	11	9	3	192	0.06
100d	0	10	7	16	3	5	10	3	23	6	27	6	11	4	7	2	12	9	11	5	174	0.05
100e	3	10	14	10	2	15	15	4	23	6	16	8	5	8	3	4	11	4	13	4	177	0.05
100f	2	10	14	10	8	11	12	5	38	7	10	7	2	12	2	7	8	3	15	4	187	0.06
100g	0	9	9	7	2	8	33	3	47	12	12	4	11	3	2	6	20	4	10	4	206	0.06
100h	0	4	3	16	3	6	51	6	35	8	9	13	7	1	1	3	15	3	8	5	195	0.06
100i	4	9	7	8	4	4	4	10	36	19	11	10	8	3	10	2	7	15	17	3	190	0.06
100j	2	8	37	11	12	25	7	0	23	5	7	7	5	2	7	2	7	0	4	0	171	0.05
101	2	8	24	16	3	3	6	6	27	16	5	7	12	0	14	1	7	11	8	8	183	0.05
102	2	21	23	4	26	0	20	13	28	7	10	14	5	2	7	1	2	4	5	3	195	0.06
Total	32	149	220	204	123	125	286	88	431	147	230	153	92	84	99	65	133	114	228	62	3360	
Frequency	0.01	0.04	0.07	0.06	0.04	0.04	0.09	0.03	0.13	0.04	0.07	0.05	0.03	0.03	0.03	0.02	0.04	0.03	0.07	0.02		

b

Residue	C	A	V	L	I	P	F	Y	W	M	G	S	T	N	Q	D	E	K	R	H
96	0.3	-2.0	1.0	1.9	0.0	-1.5	-1.5	2.4	2.7	-2.2	-0.8	-3.2	0.0	-2.0	0.0	-1.2	-1.0	2.7	6.3	4.0
97	2.0	-1.5	0.8	12.0	8.0	-1.6	0.7	0.4	-2.3	3.3	-1.6	-1.7	-1.8	-2.0	-2.2	-1.8	-2.5	-2.3	-1.1	-1.1
98	-0.5	0.6	0.3	-0.3	-0.2	-1.6	-0.3	-1.7	-1.0	2.2	0.4	0.8	0.1	-0.7	0.8	-0.2	2.3	3.7	1.8	-1.3
99	-0.5	0.4	-1.1	-1.2	-1.7	1.1	-0.6	1.7	-1.9	0.6	-0.2	-0.1	-0.8	3.3	0.4	1.5	0.5	1.8	5.4	-1.2
100	0.3	1.5	-1.7	-1.5	-0.1	1.7	-0.4	-0.7	-1.7	-0.1	2.6	3.1	0.2	-1.1	-0.4	5.9	-1.4	0.5	1.1	0.5
100a	-0.5	-0.3	2.3	-0.4	-0.1	1.3	-1.1	-0.2	0.5	-0.9	3.2	0.7	-0.7	-1.6	0.9	1.5	0.5	-2.0	1.2	-1.2
100b	1.7	0.1	-0.6	-1.4	-0.3	-0.3	1.8	-0.4	1.1	-2.8	2.9	2.2	-0.2	5.9	-1.0	-0.3	-1.2	-0.5	-1.0	0.9
100c	0.1	1.2	-3.0	-1.4	-1.5	0.1	0.2	-0.9	1.5	-1.5	4.2	0.5	-1.2	5.1	3.5	0.2	-1.3	1.8	-1.1	-0.3
100d	-1.3	0.6	-1.4	1.6	-1.3	-0.6	-1.3	-0.7	0.1	-0.6	4.2	-0.7	2.6	-0.2	0.8	-0.7	1.9	1.3	-0.4	1.0
100e	1.0	0.8	0.7	-0.3	-1.8	3.1	0.0	-0.3	0.1	-0.6	1.1	0.0	0.1	1.7	-1.0	0.3	1.5	-0.8	0.2	0.4
100f	0.2	0.6	0.5	-0.4	0.4	1.6	-1.0	0.1	2.9	-0.4	-0.9	-0.5	-1.4	3.4	-1.5	1.8	0.2	-1.3	0.7	0.3
100g	-1.4	0.0	-1.2	-1.5	-2.0	0.0	3.7	0.0	4.0	1.0	-0.6	-1.7	2.1	-0.9	-1.6	1.0	4.2	-1.1	-1.0	0.1
100h	-1.4	-1.6	-2.9	1.1	-1.6	-0.5	8.4	0.4	2.0	-0.2	-1.3	1.4	0.5	-1.8	-2.0	-0.4	2.6	-1.4	-1.4	0.7
100i	1.6	0.0	-1.5	-1.1	-1.1	-1.1	-3.0	2.3	2.4	3.7	-0.5	0.3	1.0	-0.8	1.9	-0.9	-0.2	3.4	1.2	-0.3
100j	0.3	0.0	7.7	0.2	2.3	7.2	-2.0	-2.1	0.2	-0.9	-1.4	-0.2	0.2	-1.1	0.9	-0.7	0.1	-2.4	-2.1	-1.8
101	0.2	0.0	3.3	1.5	-1.4	-1.6	-2.4	0.5	0.7	2.8	-2.1	-0.4	3.1	-2.1	3.7	-1.4	-0.1	1.9	-1.3	2.5
102	0.1	4.1	2.9	-2.4	7.1	-2.7	0.8	3.5	0.6	-0.5	-1.0	1.7	-0.3	-1.3	0.5	-1.4	-2.1	-1.0	-2.4	-0.3

FIG.44

Amino Acid Bias by Residue Type

Residue	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
96	0.01	0.08	0.01	0.03	0.09	0.00	0.16	0.05	0.11	0.08	0.03		0.02	0.05	0.14	0.04	0.06	0.06	0.02	0.11
97	0.02	0.15			0.06	0.02	0.02	0.21		0.23	0.12		0.01		0.03	0.02	0.01	0.06	0.03	0.06
98	0.06	0.05	0.04	0.10	0.05	0.06	0.02	0.05	0.13	0.06	0.10		0.02	0.07	0.08	0.07	0.07	0.06	0.04	0.01
99	0.05	0.03	0.09	0.06	0.04	0.05	0.02	0.02	0.08	0.03	0.06	0.12	0.07	0.06	0.13	0.05	0.04	0.03	0.04	0.10
100	0.07	0.05	0.21	0.02	0.04	0.09	0.06	0.05	0.06	0.02	0.04	0.03	0.08	0.03	0.07	0.11	0.05	0.03	0.04	0.03
100a	0.05	0.05	0.08	0.07	0.04	0.10	0.03	0.05	0.02	0.04	0.04	0.01	0.08	0.06	0.07	0.06	0.03	0.09	0.06	0.06
100b	0.06	0.10	0.05	0.03	0.08	0.10	0.08	0.05	0.04	0.03	0.01	0.21	0.05	0.03	0.04	0.10	0.05	0.04	0.07	0.04
100c	0.08	0.05	0.06	0.03	0.06	0.13	0.06	0.03	0.09	0.03	0.03	0.19	0.06	0.12	0.04	0.07	0.03	0.01	0.07	0.03
100d	0.07	0.03	0.04	0.08	0.04	0.11	0.08	0.02	0.08	0.08	0.04	0.04	0.04	0.06	0.05	0.04	0.11	0.03	0.05	0.03
100e	0.07	0.08	0.06	0.08	0.05	0.07	0.06	0.02	0.03	0.05	0.04	0.09	0.12	0.05	0.05	0.05	0.05	0.06	0.05	0.05
100f	0.07	0.08	0.10	0.06	0.04	0.04	0.06	0.06	0.03	0.04	0.04	0.14	0.08	0.03	0.07	0.04	0.03	0.06	0.09	0.05
100g	0.06		0.08	0.15	0.11	0.05	0.06	0.02	0.04	0.04	0.08	0.03	0.06	0.02	0.05	0.03	0.11	0.04	0.10	0.04
100h	0.02	0.03	0.05	0.12	0.18	0.04	0.08	0.02	0.03	0.08	0.05	0.01	0.05	0.02	0.04	0.08	0.07	0.01	0.08	0.06
100i	0.05	0.10	0.04	0.05	0.01	0.05	0.05	0.04	0.14	0.03	0.13	0.04	0.03	0.10	0.08	0.06	0.08	0.04	0.08	0.10
100j	0.06	0.05	0.03	0.05	0.03	0.03	0.13	0.09		0.06	0.03	0.02	0.19	0.06	0.02	0.04	0.06	0.16	0.05	
101	0.06	0.05	0.03	0.06	0.02	0.02	0.13	0.02	0.09	0.08	0.11		0.02	0.15	0.03	0.05	0.13	0.10	0.07	0.06
102	0.13	0.05	0.03	0.01	0.07	0.04	0.05	0.21	0.03	0.02	0.04	0.02		0.08	0.02	0.09	0.06	0.11	0.06	0.14

Standard Deviations above Average

> 2
> 1.5
> 1

FIG.45a

Percent Abundance Round 3 Round 4	CDR3 Sequence																
	96	97	98	99	100	100a	100b	100c	100d	100e	100f	100g	100h	100i	100j	101	102
3.9	R	I	G	R	S	V	F	N	L	R	R	E	S	W	V	T	W
10.5	L	L	R	R	G	V	N	A	T	P	N	W	E	G	L	V	G
3.3	V	L	R	R	R	V	N	S	V	A	I	F	E	R	V	Q	S
8.3	R	L	K	R	G	G	S	S	L	V	S	W	T	M	P	L	A
6	R	L	V	N	P	L	S	G	R	V	S	E	P	S	G	V	A
4.1	F	V	A	G	R	W	W	W	L	W	R	P	W	M	S	L	A
3.8	V	L	E	L	R	S	S	G	R	N	A	T	W	S	S	L	Y
2.2	L	R	I	S	P	Y	A	F	G	L	G	R	W	A	P	S	Y
1.9	L	W	T	R	A	R	S	W	W	W	W	W	W	R	E	Q	F
1.3	W	R	S	W	I	S	S	I	R	L	L	R	R	W	W	Y	A
1.3	K	S	T	R	W	R	A	G	H	G	R	T	E	H	W	L	S

FIG. 45b

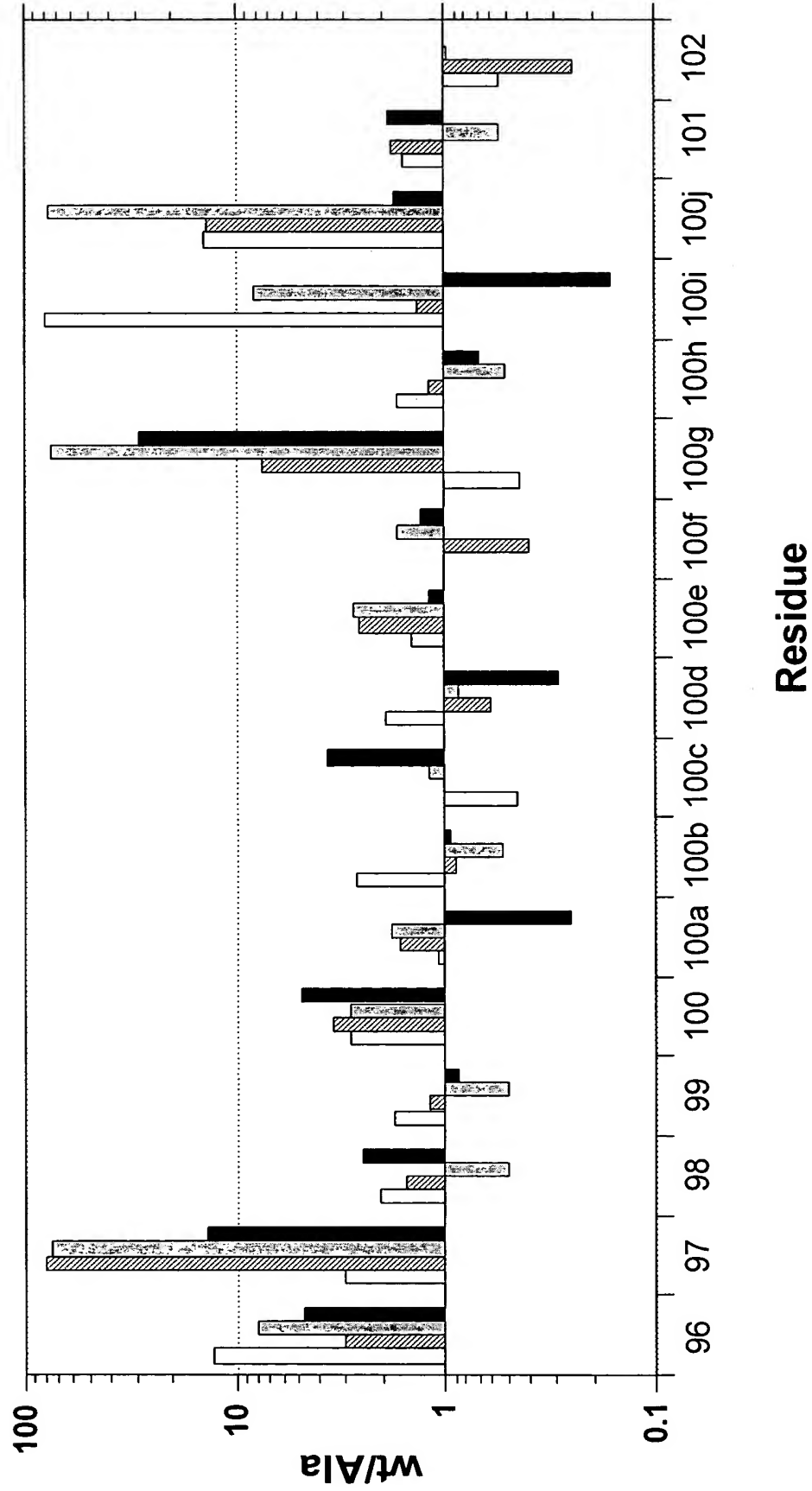


FIG.46

Distribution of Loop Lengths

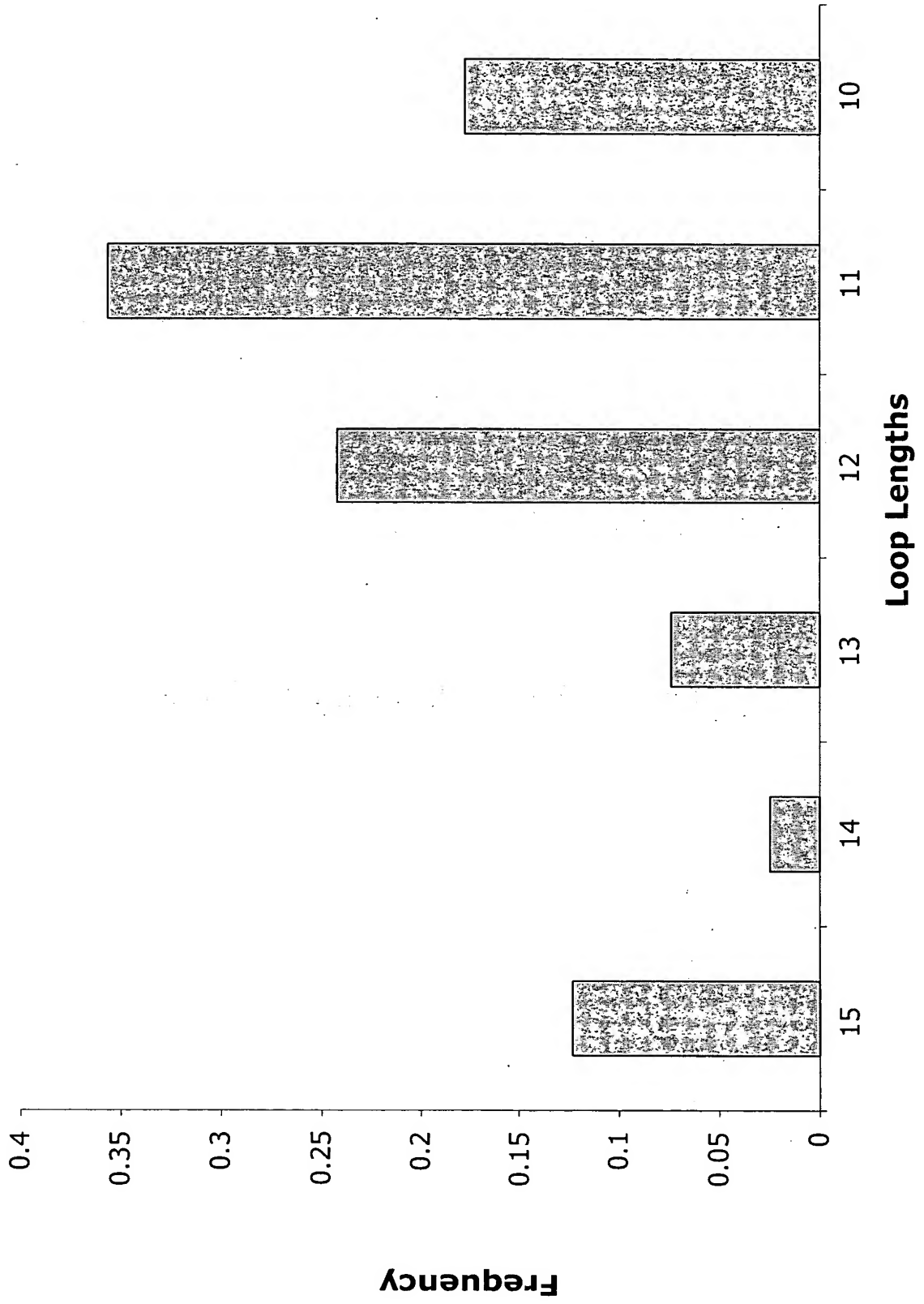


FIG. 47

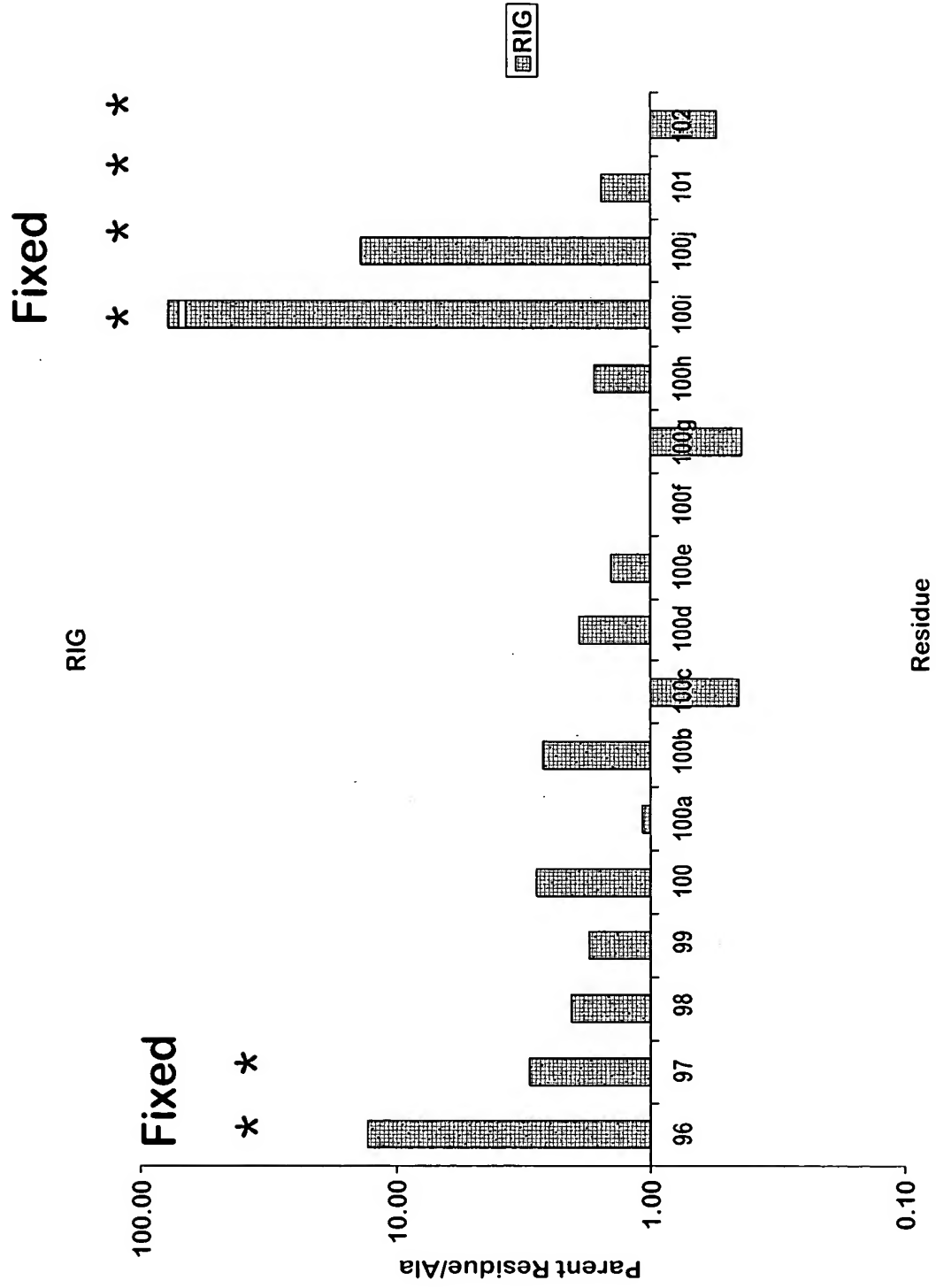


FIG.48

Residue	C	A	V	L	I	P	F	Y	W	M	G	S	T	N	Q	D	E	K	R	H
98	3.36							4.36	2.69		-1.07	-0.26							4.76	
99	5.21	0.33						-1.84	-0.78		-1.16	-1.55		0.72						
100	0.41	-1.73						0.55	2.42			0.14		0.81						
100a	-0.66	1.74						0.84	-2.18		2.97	-1.94		0.96		3.45				
100b	0.51	0.47						1.82	0.95			-0.87								
100c	-1.85	0.77						-0.09	1.39		1.83	-0.64	0.15			3.69			1.94	
100d	-1.69	-0.28						0.21	-1.99		3.57	0.81		1.30						
100e	-1.58	-0.17						-2.40	1.87			2.95	0.38	4.95						
100f	0.21	-0.06						-2.26	-1.83		2.47	-0.17	11.51							
100g	4.30	0.46						-1.72	-0.66			-0.91	0.02			3.29				
100h	-1.51	1.22						0.52	-1.87		0.79	2.44		1.54						

FIG.49

2 Point Competition Elisa

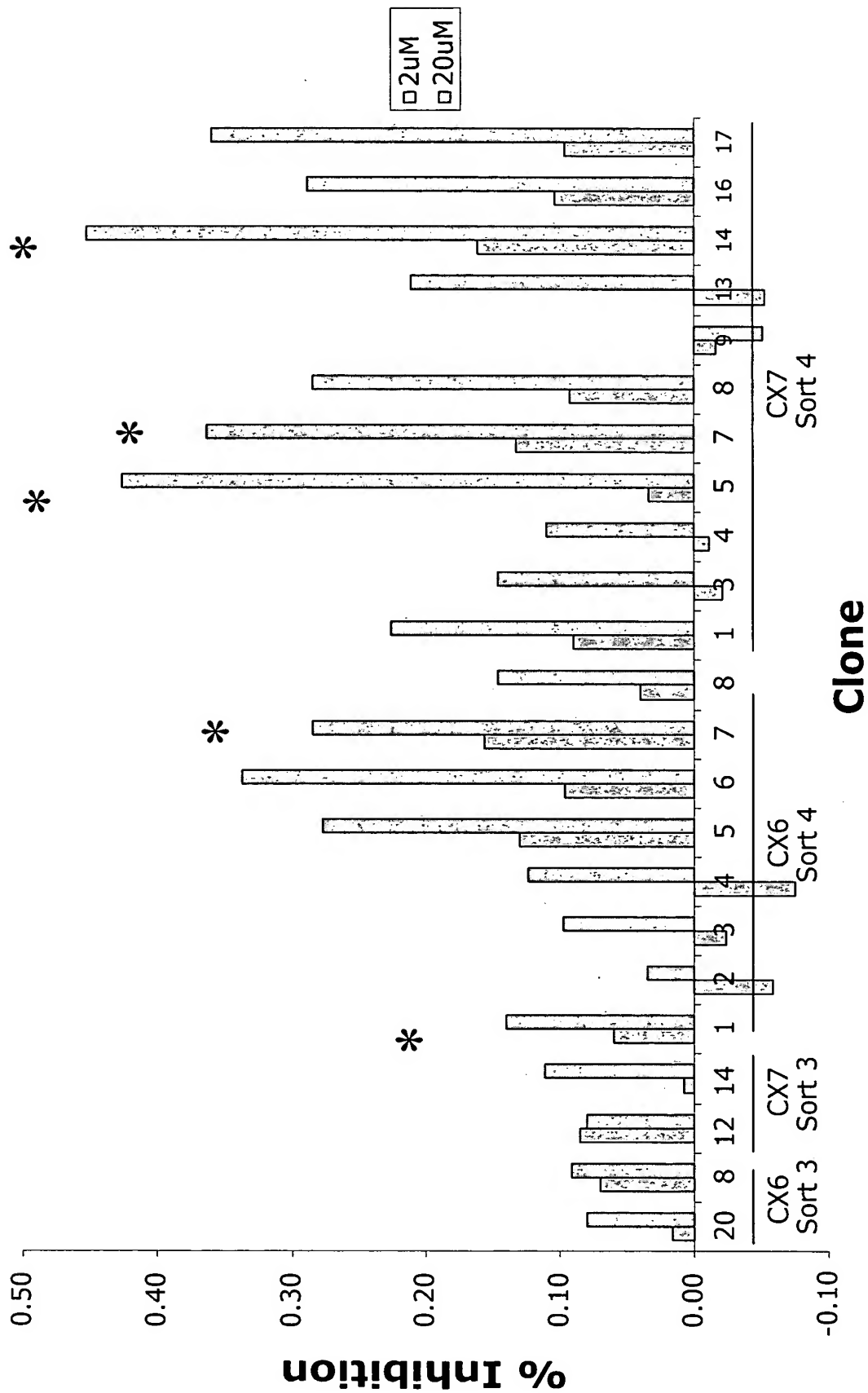


FIG. 50

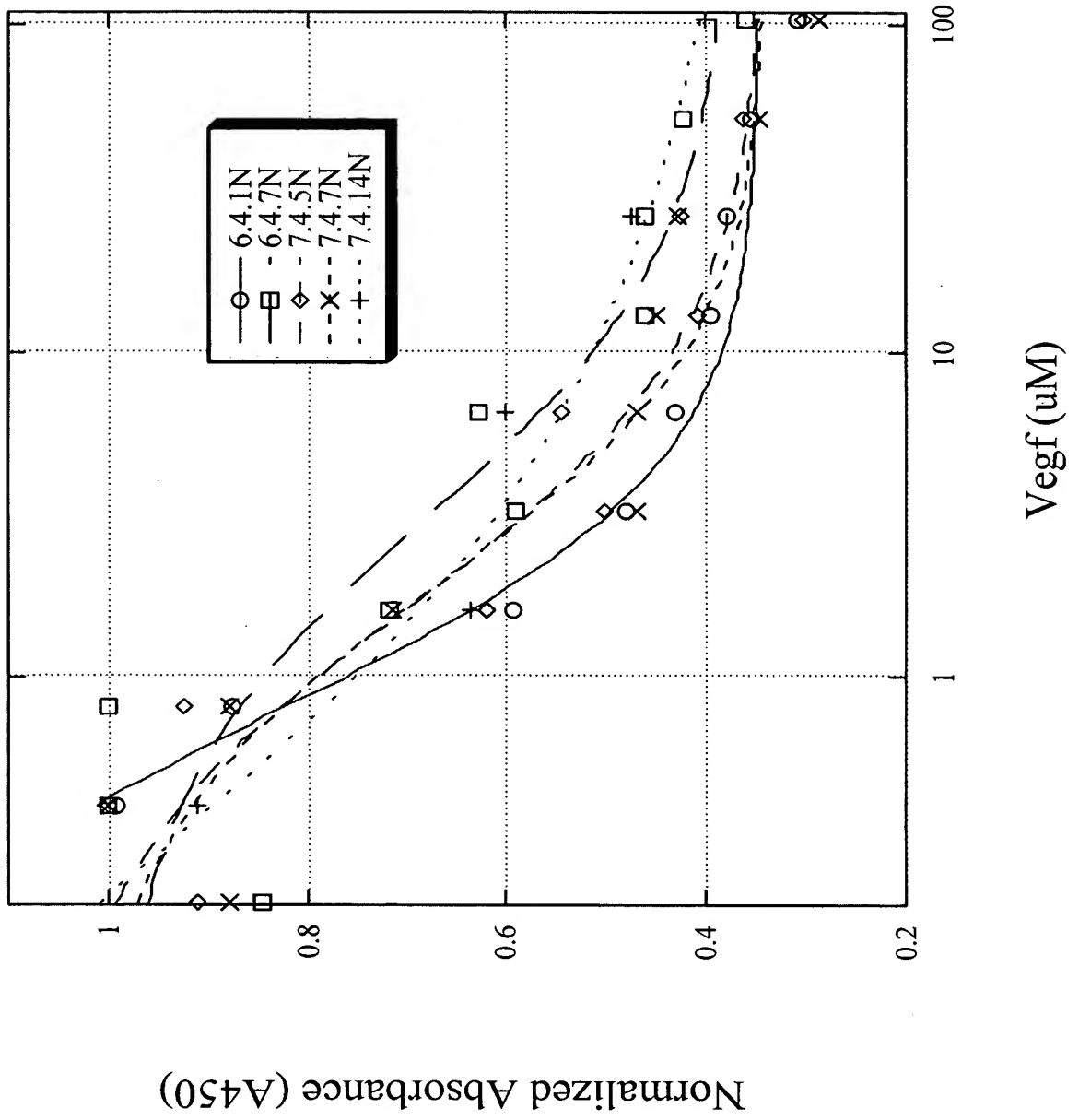




FIG. 51

FIG.52

Residue	C	A	V	L	I	P	F	Y	W	M	G	S	T	N	Q	D	E	K	R	H
37	1.2 #####	0.5	-0.7 #####	1.4	3.5	#####	0.0	#####	#####	#####	#####	1.2	#####	#####	#####	#####	1.2	#####	#####	#####
45	#####	1.0	-0.1	0.2	#####	1.8	#####	#####	-1.2	1.2	1.3	#####	#####	#####	#####	#####	#####	3.0	#####	#####
47	#####	0.7	0.3	1.3	#####	0.0	1.3	#####	-1.5	2.2	0.2	0.2	#####	#####	1.5	#####	#####	#####	-0.8	#####
91	#####	#####	#####	-0.7	1.6	#####	0.5	0.1	-1.5	#####	#####	0.2	4.3	1.6	#####	#####	#####	#####	-0.4	1.6

FIG. 53

